IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC, Plaintiffs, v. BARR LABORATORIES, INC., Defendants.	: : : : : : : : :	Civil Action No. 06-286-GMS

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Wilmington, Delaware
Monday, May 19, 2008
11:00 a.m.

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BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

APPEARANCES:

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Ashby & Geddes
-and-
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THE COURT: Good morning. Please be seated. Let's start with a round of reintroductions.

MR. DAY: Good morning, Your Honor.

THE COURT: Good morning.

MR. DAY: On behalf of the plaintiffs, we have John Day from Ashby & Geddes locally. At counsel table Paul Berghoff, Joshua Rich and Jeremy Noe.

In our second row, Your Honor, also from McDonnell Boehnen, Allison Baldwin, and the senior director of global patent litigation for Sanofi-Aventis, Peter Dolan.

Providing our technical support, Eric Pubins, next to him is Andrew Williams, also from McDonnell Boehnen.

And finally, back of the well, from McDonnell Boehnen, Aaron Barkoff, Scott Miller, Nicole Lammers, and Rory Shea (phonetic).

THE COURT: Good morning.

MR. DAY: Thank you.

THE COURT: Counsel.

MS. PASCALE: Good morning, Your Honor. Karen Pascale from Young Conaway for Defendant Barr Laboratories. I will introduce my trial team from Winston & Strawn. Jim Hurst. Maureen Rurka. Taras Gracey. Also in the courtroom Julia Johnson and Renee Sofos.

THE COURT: Good morning.

MS .PASCALE: Thank you, Your Honor.

THE COURT: Thank you. All right.

Counsel, I would benefit probably from a small opening. You don't need to do a jury speech.

MR. BERGHOFF: Thank you, Your Honor. That is what I had in our mind, just a small laying-the-groundwork opening statement.

If we could pull up the slides there.

The case is about Nasacort AQ, what is in this little box that the patient would get, more importantly, what's in the bottle and the bottle itself, working as a unit to deliver the intranasal spray to a patient's nose, where it's indicated to treat allergic rhinitis, among other

conditions.

Just a few basics about Nasacort AQ. It is an aqueous intranasal spray. That is more or less a term of art in the area. It distinguishes it from sprays that are solutions and, in fact, it's used to indicate that the spray is a suspension. And we will talk a little bit more about that in the opening, and certainly quite a bit about that during the trial.

It is indicated for the treatment of nasal symptoms of both seasonal and perennial allergic rhinitis. I just think of it as allergies. I think that is probably a good enough approximation, although we will have some testimony from physicians shedding a little more light as needed on that portion of the case.

The active ingredient is a steroid, particularly a corticosteroid.

This one is called tramcinolone acetonide. I believe that we will be able to refer throughout this trial to that active ingredient simply as TAA. That's going to be my plan, because two out of three times I trip when I try to pronounce the full name.

Anyway, Nasacort AQ is a very successful drug for Sanofi-Aventis.

I should stop and say that sometimes people pronounce that Sa-no-fa. I say Sa-no-fee. I am not sure

who is right. It's a French name. It's probably somewhere in between. I cannot correctly pronounce it anyway. It is a very successful drug for Sanofi-Aventis. Probably 300 million dollars in U.S. sales every year, and has sold over 2 billion dollars to date in the U.S., all for the treatment of nasal allergies.

Now, some of the relevant properties of Nasacort AQ that we will be discussing through trial and our witnesses will be, hopefully, providing help to Your Honor, is listed on this slide.

The first is, I have already mentioned, it is a suspension. A suspension is really nothing more, as I understand it, than particles that are suspended in a liquid. In other words, they don't settle out to the bottom. But they are still particles. It's not like sugar dissolved in our water.

That's a solution. This is actually with the particles that are staying in place in the liquid. Not settling out.

The property of the suspension of Nasacort AQ is important to its stability.

If the particles settle out to the bottom of bottle, we now have a dosing problem, because there might be very little medicine up top. It all might be sitting on the bottom. Maybe it will get redistributed when the patient

shakes it, if they follow the directions. But it's important to have that suspension be stable at all times, because the particles that are suspended are the active ingredient, the TAA.

Another important feature of Nasacort AQ, like it being a suspension, is the subject of the claims that we will be discussing, is, as Your Honor may appreciate from our Markman hearing, is its thixotropy, or the fact that Nasacort AQ is thixotropic. Thixotropy -- I will leave that for the experts to discuss that in more detail -- but in the context of this case it simply means that the liquid and particles are thick when they are allowed to rest, or when they are in an unstressed state.

I will give you an example of what stress would be (indicating). That would be stress. But in an unstressed state --

THE COURT: You were shaking it.

MR. BERGHOFF: If I left the bottle sit, or in the nose, it would be relatively thick.

In a stressed state, though, whenever I do anything to it that's going to disturb it, of any significance, shaking, stirring, pouring, you name it, adding stress to it, a thixotropic liquid of this type will get thinner. It will get less viscous. And in terms of numerical measurements, the viscosity of the suspension, the

liquid and the particles, will actually go down. Then when the stress is removed, the viscosity, the thickness, will return. Not immediately. In fact, that is actually part of the understanding of what it means to be a thixotropic composition. The viscosity returns over time.

We will hear more about that.

Nasacort AQ, as defined in the claims, has a specific viscosity profile. It's referred to in the claims as thixotropic properties. We will talk much more about this during the case. In general, it goes from a relatively high viscosity, when measured according to the patent, to a relatively low or thinner viscosity, when it's subject to shearing or shaking, and then returns to that relatively high viscosity.

The relatively high viscosities are referred in the patent as the setting viscosity, because the material has a chance to set up, maybe not a hundred percent, but it gets back enough that it is able to hold all those particles in suspension and be a thicker material, which has some significance for the application of the drug to the nasal mucosa, to the nasal surfaces.

The specific viscosity profile is laid out in the claims in the patent. In the claims that we have narrowed the case to -- and I think Your Honor may be happy to hear that we have focused this trial down to just two

claims, one claim from each patent, and I will walk through those in a little detail in just a moment.

Just as a note, we did that narrowing of claims, selection of claims, based on Your Honor's Markman ruling. And should things change and we be back down here again with a different construction, rumor has it that could happen, just in theory, Your Honor, we may have a different set of claims based on that construction.

But for now, we are cutting it down to just the two.

In the claims that we are presenting at this trial, the setting viscosity is defined as being 400 and 800 centipoise. We will hear from the experts what that means. But that is the measurement for viscosity. And the shear viscosity is set at a lower level of 50 to 200.

Odorlessness is one of the features of one of our claims that we are asserting, that the product is odorless. That has been defined by agreement between the parties as, I have the quotes up on the slide, odors that cause the user discomfort are absent.

So it is not a hyper-technical definition of odorless. I have been told nothing is truly odorless. Everything has a little odor.

What we are talking about in the claim, in the invention here, is odors that cause user discomfort. And

Nasacort doesn't have those.

The reason it doesn't have it, as will be clear from the evidence, it doesn't have a compound called phenyl ethyl alcohol. Phenyl ethyl alcohol was used in prior aqueous nasal suspensions in the prior art and has a significant smell that many patients find unpleasant, and that causes burning and irritation because it's an alcohol.

Nasacort does not use phenyl ethyl alcohol. And we believe the evidence will show that was a significant advance in the art. Now, Nasacort AQ is covered by two patents. The '573 patent, I think that is how the parties will be referring to that one, we have marked that as Plaintiffs' Trial Exhibit PTX-1, and the second patent is the '329 patent, this one issued later. Both have the identical text, except for the claims, of course.

My plan is, when I am looking at the text of the patents, to just refer to the earlier one, PTX-1, the '527 patent.

Both patents, of course, because they have identical text, disclose the exact formulation for Nasacort AQ. It is right there in Example 1. It's described as a preferred pharmaceutical composition. But, in fact, that is an exact recipe for Nasacort AQ.

And the evidence, we believe, will show, Your Honor, that Barr's ANDA product which we are accusing of

infringement in this case is an exact copy of, take your pick, Nasacort AQ and Example 1 in our patent. It has the exact formulation. There is one ingredient that varies by one in the fourth decimal point. That's how close it is. It is an absolute virtual copy.

The history of the accused product will be presented to Your Honor in the form of exhibits that may be cited in the posttrial briefing, deposition testimony, which Your Honor will review as directed in the posttrial briefing, and some witness testimony. But because we aren't going to hear a full explication of this live, I did want to spend just a little time on the history of the accused product.

It began with a company named Agis, and Agis in the 1997-'98 time frame began working on developing a generic version of Nasacort AQ, of the formulation. And skipping forward to Agis as related to this case, in August of 2003, Barr signed an agreement with Agis by which Barr obtained the rights to file an Abbreviated New Drug Application with the FDA, based on Agis's Nasacort generic formulation and to market that formulation.

So that's the relationship of Agis and Barr.

Beginning, the documents and deposition testimony show us, beginning in 1997 and '98, Agis spent at least 14 months attempting to reverse engineer Nasacort AQ

and to validate a generic version of that formulation, to get it ready for possible filing by somebody to the FDA.

And what do I mean by reverse engineering? Well, they obtained lots of these bottles and analyzed it and repeatedly tried to make recipes, formulations, that were as close as possible, if not identical, to Nasacort AQ.

And what they ended up with, after this 14-month effort on their part, was not an exact copy. It was close. It was close. But there were some differences in the formulation, especially in the amounts of a couple of the ingredients.

They got, let's say, 94 percent of the way there with their reverse-engineering effort.

Agis then took this close copy, made three fairly large-scale batches, and then -- and you would make large-scale batches like this for submission to a regulatory agency like the FDA, and then they simply stopped development of the product. And it lay fallow, the documents and testimony show, for about three years.

And then Barr comes into the picture, signs the deal in 2003 with Agis, and then in late 2003, after Agis had now begun again to look at its copied formulation, Agis and Barr actually abandoned the reverse-engineering efforts that they had undertaken, that had gotten them close but not exactly the same as Nasacort AQ, and just made an exact copy

of Nasacort AQ, taking the formulation directly from the patent, directly from Example 1. It was actually the second patent, I believe, the '329 patent. But it's the same thing.

So a lot of effort to reverse engineer it, followed by eventual, just dead-copying of the patented formulation.

As I had mentioned before, Your Honor, we have two claims at issue. Claim 6 of the '573 patent and Claim 26 of the '329 patent. I will put the language up in just a moment, and we can see where the disputes lie as to infringement.

But the parties, I think, have done a good job in trying to minimize the number of words in the claim that are going to be in dispute for infringement.

This is Claim 6 of the '573 patent. Maybe the bolding doesn't show up quite as clearly as I had hoped. But the bolded words are what are in dispute. They relate to the thixotropic properties. And they relate in general terms to how the product deposits on the nose.

So we are going to have testimony certainly during our case-in-chief that is going to focus on the thixotropic properties of the compositions at issue here, as well as how the product, how Nasacort AQ, deposits on the nose. And specifically, there will be a lot of focus on how

it deposits in one part of the nose, called the frontal sinus. We will have testimony that will guide all of us, I am sure, on understanding some nasal anatomy, so we can see what is at issue on the issue of deposition or not.

If we go to the next claim, this is Claim 26 from the '329 patent. Many, not quite all, but many of the same issues that were in dispute with Claim 6 will be in dispute with Claim 26 of the '329 patent.

But there are at least significant chunks of the claim that the parties agree are there. And we won't have to introduce proof on them.

We believe that the evidence will show that Barr's ANDA product meets every element that is contested of these two claims, including the specific thixotropic properties. We will introduce evidence to show that. We think it's clear that it is odorless. It's the same formation as Nasacort. Nasacort is odorless.

We think it will be clear from the evidence that it does, in fact, deposit on the frontal sinus. This is the one area of the nose that is in dispute. And it is retained on the frontal sinus for a sufficient period of time as called for by the claim. And the claims require that it resist mucociliary clearance.

Let me just talk about those last two just for a moment.

The issue is that Barr says, when Nasacort is sprayed into a patient's nose, it doesn't make it to the frontal sinus. We have evidence it does. Barr says when Nasacort is sprayed into the patient's nose, it doesn't stay on the frontal sinus long enough. We have evidence that shows it does. And that same evidence that shows that it stays on the frontal sinus is the same evidence that will show that it is, in fact, resisting mucociliary clearance, which, in the absence of a viscous formulation, clears things out very promptly, sometimes on the order of 10 to 15 minutes.

We have evidence that this formulation, Nasacort, and therefore Barr's copy, stay on the frontal sinus deposited there for an hour or more, certainly enough to constitute resisting mucociliary clearance.

We have testimony that will show Barr's ANDA product has the properties of the claims. Dr. Lockhead actually tested Barr's product and Nasacort. And Dr. Prud'homme -- both of these are experts in viscosity -- the fancy word is rheology, but for our purposes they are experts in viscosity. Dr. Prud'homme will then link Dr. Lockhead's testing to the language of the claims, to establish that, indeed, Barr's product meets those limitations.

As to the odorless feature, Dr. Meltzer, a

physician, expert in allergies, will testify that Barr's product, just like Nasacort, is odorless in that it doesn't have odors that cause patient discomfort.

Dr. Berridge, who is an expert in positron testing of the nose, PET testing, very cool stuff, very high-tech stuff, will be here to describe the tests that he did on the deposition pattern, where Nasacort deposits in the nose. And that testing will clearly show that it deposes in the frontal sinus and is retained there for a sufficient time, such that it resists the naturally occurring mucociliary clearance process that is in everybody's nose, trying to clear particles out as quickly as possible.

Dr. Berridge's evidence will show that, in fact, Nasacort AQ and therefore Barr's copy makes it to the frontal sinus and is retained there. And therefore, since Nasacort does it, although we don't have testing of Barr's product by PET, if Nasacort does it, Barr's product will do it, too, because it's a dead-copy.

And because it resists mucociliary clearance, it is really going to be Dr. Berridge's evidence as well, because if it stays on the frontal sinus, as his testing shows, well, that means it is resisting mucociliary clearance.

If it stays around for a period of time longer

than the normal clearance time, it's resisting clearance.

And then Dr. Meltzer will summarize, just so it's all in one place, Your Honor, that, indeed, Barr's ANDA product has all of the elements of the claim, all of the disputed elements. And we believe that we will easily meet our burden of proof by a preponderance of evidence on the infringement issue.

I do want to turn to invalidity, but just very briefly, because I am not a hundred-percent sure of the case we will see on invalidity and I don't necessarily want to address issues that aren't going to be addressed.

I will just address it shortly at a very high level, that I am confident, regardless of how the evidence comes in, my comments will be meaningful. At least that's my hope.

The patent, of course, presumed valid. The burden is on Barr, clear and convincing evidence.

An issue that Barr is arguing in this case is that our Phase 3 clinical trials, the clinical trials by Sanofi-Aventis -- it was actually a predecessor company of Sanofi-Aventis, Sanofi has gone through a number ever mergers, but it is the same company coming forward with different names -- that those clinical trials were not a public use.

We believe that the evidence will be clear that

these clinical trials were conducted in confidence, that the patients who engaged in the clinical trials were given very limited information about the product they were testing. It was Nasacort AQ, but all they knew was, possibly, was the identity of the active ingredient. They didn't know anything about the formulation. Nothing.

And they were given very small amounts, just what they needed, to conduct the test. And those samples had to be returned under Federal law and accounted for.

So very tight controls were maintained by the predecessor company, whose name you will hear from time to time in the case was Rhone-Poulenc Rorer. And we will shorten that to RPR. But RPR maintained very tight control over the clinical trials at all times.

And there was absolutely no commercial exploitation going on. These were Phase 3 clinical trials.

So we believe when the evidence is all received into evidence, and viewed under the totality of the circumstances standard for public use, that all of the factors, all of that, will point towards it not being a public use.

We believe that the prior intranasal sprays that Barr is relying on as prior art do not render the patent claims obvious.

There is no anticipation issue in this case,

Your Honor. It's all just about obviousness.

And we believe that, and this is not a full list, but we believe that at least these prior art sprays lack important claim properties:

Odorlessness. As I mentioned, the prior art, aqueous and intranasal sprays were decidedly not odor-free. And they also lack the specific viscosity properties called for by the claims: the specific, the unique viscosity profile.

We believe there will be evidence on the obviousness issue of objective indicia of nonobviousness, so-called secondary considerations, of course, and we will have quite a number of them listed hereto:

Copying by others. We already talked a little bit about the copying by Agis, but there are other examples of that.

Failure of others, long-felt need. Nasacort AQ provided unexpected results, going against the grain of conventional wisdom. And,

Commercial success. You already saw our sales numbers but there certainly will be evidence tying those sales to the claimed properties of Nasacort AQ. And we believe that Barr will not carry the entire burden of proof on invalidity.

I will check with Eric. Is that my last slide,

Eric? Yes, it is. Thank you, Your Honor.

THE COURT: Thank you. We're going to work this afternoon until about ten minutes to 1:00 and then we'll come back. We'll take an hour break and then come back.

Counsel.

MR. HURST: Thank you, Your Honor. Just briefly, Your Honor, in our introductions we neglected to introduce our client who is here from Barr Laboratories: Azeen James, who is the Vice President of Intellectual Properties; and Bridget Cooney, who is an in-house litigation lawyer as well.

THE COURT: Okay.

MR. HURST: I want to, Your Honor, talk about and focus on the issues that are going to be decided by Your Honor. And we have four defenses: non-infringement, enablement, obviousness and anticipation based on prior public use.

And I'd like to start just with noninfringement. There are multiple reasons our product does not infringe, but I want to start with the fact that Barr's product does not reach the frontal sinus as required by the claims. This I imagine was one of the claim construction issues that counsel referred to; but in the only two asserted claims, there is the phrase "the mucosal surfaces of the nasal cavity" which has been construed to include the frontal

sinus. Claim 26, one of the two claims asserted actually says it expressly: a method for delivering the nasal spray to the frontal sinus.

Now, let me tell you what you are looking at here on this slide. We're going to have a medical doctor and a surgeon, Dr. MacKay explain this in some detail, but just briefly. He has actually conducted countless frontal sinus surgeries so he has seen it firsthand.

Here is the important point, Your Honor. There is not a straight shot from the opening of the nose to this isolated cavity up here which is the frontal sinus. The pathway to the frontal sinus is meandering. It's somewhat tortured. To get to that frontal sinus, you have to go through this little hole right here. This is the turbinate. This is the turbinate. Go through there. And when you are behind there, this is what is behind the turbinate. This is an x-ray scan. There is a pathway right here. Right there. And then after that pathway, there is something called the frontal ethmoidal recess, and then you get to the frontal sinus.

Now, here is the important point. And this is what we think the evidence is going to show. These nasal sprays, they stay where they spray. That is the Nasacort marketing pitch: They stay where they spray. And that's true. The spray droplets, they're not marbles or beads.

They don't bounce around the nose. They hit where they stick. Wherever they hit, they stick. And so what happens is the spray is expelled fairly rapidly from the bottle, and wherever the spray droplets hit, that is where they stay.

For a spray droplet to get to the frontal sinus, it would have to do this. It would have to go through here, to go through that little hole I mentioned from the turbinate, which isn't shown here, this direction; would have to make a U-turn, go up this pathway.

Now, remember, the people that are using the nasal spray, they're stuffed up. They're congested. They're inflamed. So that pathway is going to be narrower than it is. This is a healthy person so it's going to be narrower. And there is cilia there, nasal cilia. There are protrusions that aren't shown. So the spray droplet, without hitting any surfaces, would have to make this U-turn, get all the way up that pathway, through the frontal ethmoidal recess -- again, without hitting a surface; because it hits, it sticks -- and then get to the frontal sinus. And we think the evidence is going to show that that is not possible. It's just not possible. And it's not realistic.

Now, you really don't have to rely on -- just looking at the structure of the frontal sinus probably tells you as much as you need to know. But you can also look at

Aventis's testing. Aventis's testing shows that the spray droplets don't do the gymnastics required in this U-turn in the air without hitting surfaces that is required to get to the frontal sinus. Aventis did testing in 2002, this PET-scanning testing, and they showed that in the frontal sinus they detected literally zero deposit with their product, Nasacort. Literally zero deposit. Nothing. No uptake was observed in the frontal sinus. A bunch of other places where the drug was observed but zero in the frontal sinus. So that is before the litigation.

Now, during the litigation, they have reconstructed a series of three studies to make the following argument:

Of the 14 patients who were studied -- in 1996, 1998 and 2002, of the 14 patients that were studied, one of Aventis's experts is going to say, well, we found trace amounts in the frontal sinus, the gymnastics occurred that I was talking about, for 6 of the 14 patients.

Now, we do think that the argument is based on: Number one, a flawed study design. Number two, just mere background noise. Nothing is perfect. There is background noise with these studies. So there was no frontal deposit. I mean you know that from the anatomy itself. But they're going to argue that 6 of 14 patients showed some trace amounts of deposit in the isolated frontal sinus cavity.

Now, let's assume that that is true. Remember, Aventis's burden for infringement is to prove that we actually infringe. There is no direct infringement. Right? Because Barr doesn't actually deliver its product to anybody's frontal sinus. We just sell a nasal spray. That is what we plan to do, we hope to do: sell a nasal spray.

There would be no contributory infringement, right? Because our nasal spray has a substantially noninfringing use even according to Aventis's best argument. Over half the people do not show any evidence of frontal sinus deposit. So there is no contributory infringement. No direct, no contributory.

And there certainly is no inducement to infringe, right? Inducement requires that Barr intends to induce people to use this product in a way that it hits the frontal sinus. I mean we don't even believe it happens, okay? There is no document, there is no testimony, there is no evidence.

And to what end? Even if a trace amount got in the frontal sinus somehow someway without hitting any other surfaces on the way, what medical benefit would there be? There is no evidence there is any medical benefit to trace amounts of drug in the frontal sinus.

The reality, Your Honor, is that when people have inflammation in the frontal sinus, I mean it's painful.

It's painful stuff. And they get treated with antibiotics that they take in their mouth. And if it's bad enough, they get surgery. That is what Dr. MacKay is going to explain. If somebody could make a nasal spray to get drug into the frontal sinus, they could print money. And nobody has ever done it, and I imagine maybe nobody ever will because of the gymnastics required. And certainly Aventis hasn't done it. So there is certainly no frontal sinus deposit at all.

Now, that alone should end the case because both claims require frontal sinus deposit. I want to skip ahead. I want to focus on two of our noninfringement defenses but I want to skip ahead to enablement, Your Honor. And the reason I want to do that is because the lack of enablement defense is a mirror image of our non-infringement defense on frontal nasal, frontal sinus deposit.

You are going to hear from Dr. Maureen Donovan. She has 20 years experience in pharmaceutical formulation with a special expertise in nasal sprays, and she has read the patent. And the opinion you are going to hear from her is this patent just teaches standard nasal sprays. It's Nasal Spray 101. It doesn't teach somebody to make a special nasal spray that creates droplets that do the U-turn and gymnastics required to get to the frontal sinus. And she is in this business. I mean she knows nasal sprays. It didn't happen in the prior art and it certainly didn't

happen with a breakthrough in this patent. It's just the standard nasal spray.

Now, she is a pharmaceutical formulator. This patent is a pharmaceutical formulation patent. It's a nasal spray formulation patent. Aventis is bringing nine witnesses to this proceeding, multiple experts; not one pharmaceutical formulator. None. We're the only party bringing pharmaceutical formulators to Your Honor to address the pharmaceutical formulation issues.

Here is just one point on enablement, Your Honor. You have to teach an ordinary, ordinarily-skilled scientist how to practice not a little sliver of the claims range, of your claims but the full scope of your claim.

Now, here is what the claims talk about: This viscosity that counsel talked about, it comes from the thixotropic properties. It comes from a mixture -- I'm going to say it. I'm going to call it MCC and CMC. It's just that mixture that creates the viscosity profiles.

Well, the claims in the patent are fairly broad. We cover any nasal spray with the range where that mixture makes up anywhere from one percent to five percent of the total formulation. And, further, we claim a mix between the MCC and the CMC where that ratio between the two, the MCC is anywhere from 85-to-95 percent of the mixture of the two where the remainder would be CMC. Okay? So that is the

range.

The testing that occurred with Nasacort is a little thin slice. It's two percent and it's 85 percent. And they have one of the --

MR. BERGHOFF: Your Honor, I obviously hesitate to stand up during counsel's presentation but this is a brand new argument we never heard of before in the case. So I would just like to lodge an objection to this argument being made.

THE COURT: Counsel, do you want to address that?

MR. HURST: We've been, throughout the case, arguing a lack of any enablement for any portion of the claims. So this is the argument we've been making throughout the case.

MR. BERGHOFF: The only argument they actually have made is the one that counsel has stated before about frontal sinus. And there is no reference to this in --

THE COURT: Speak up, counsel.

MR. BERGHOFF: There is no reference to this in any of their prior interrogatory answers.

THE COURT: Well, when you say?

MR. BERGHOFF: Or in the pretrial order either, Your Honor.

MR. HURST: It is throughout our ...

THE COURT: Could you just show me where?

MR. HURST: Yes. Our expert's opinion is that the patent teaches.

THE COURT: He has just referenced one thing that I think is readily obtainable, and that is the pretrial order.

MR. HURST: The pretrial order?

THE COURT: Yes. The point being if the arguments were made, they certainly would appear there.

MR. HURST: Yes.

(Pause.)

MR. HURST: I'll move on so we don't take up Your Honor's time.

THE COURT: All right. We'll looking for it as well.

MR. HURST: I skipped ahead to enablement because of the frontal deposit argument so let's go back to non-infringement. I just want to focus on two of the noninfringement defenses because I think they're fairly clear and straightforward.

The first is frontal sinus. The second is Barr's product doesn't match the requirement for deposited viscosity, Your Honor. Here is what I mean by that. The claims require that after the spray, after the spray is introduced into the nose, that thickens up. When you

shake it and spray it, it thins up. And then when you put it in the nose, the claim requires that the viscosity of the composition thickens up back to its setting 400-to-800 centipoise; and that is for the both of the asserted claims based on your Markman ruling.

And so here is the question that you need to ask: When Barr's product is sprayed up the nose, does it return to its setting viscosity? Well, you first have to ask how long is it in there? How long is Barr's product in the nose? Does it have enough time to return to its setting viscosity?

The patent tells you that the nasal cavity is very efficient at removing things. The patent says things are removed within 10-to-30 minutes. Let's take 30 minutes just for the sake of argument. So now the question is, is that enough time for Barr's product to return to setting viscosity while in the nose? It's not enough time, Your Honor, according to Aventis's own testing to return to setting viscosity even on tabletop.

Here is Aventis's testing. They tested their own product and said to themselves, okay. We shake it up. How long will it take to return to setting viscosity? It takes hours and days -- literally, days. Literally, days. And that might seem surprising but it's not when you know how all of this works.

The viscosity of a material is from its molecular structure. It builds a structure within the confines of the liquid to make it firm. And that's what gives it its thickness when it builds this structure. When you stir it or shake it or pour it, that structure breaks apart, it shatters. And so for it to return to its thicker setting viscosity, the molecular structure has to rebuild itself. And it can take an awful long time, depending on the composition at issue. Some compositions return more quickly than others. But the compositions that we're talking about, Nasacort, literally after five days, still had not returned to setting viscosity. It starts to return but it doesn't get anywhere near its setting viscosity for an awfully long time. So it certainly doesn't happen in 30 minutes, Your Honor.

But here is a point where I think there is a complete absence of evidence on this. Regardless of what happens on the tabletop -- and Barr's product will not return to setting viscosity within 30 minutes on the tabletop, but certainly it's not going to return to setting viscosity in a nasal environment. And that is what is at issue because that is what the claims require.

Here is the standard from the Federal Circuit, just for some context:

Evidence of in vitro testing, out of the body on

the tabletop, is irrelevant absent that the in vitro system is a good model of actual in vivo in the body behavior.

So to prove up infringement, what Aventis had to do was show that in the nasal environment -- you could create a model or something -- that in the nasal environment, Barr's product would return to setting viscosity within the 30 minutes that remained in the nasal cavity. And they didn't conduct any such testing; a complete absence of testing.

Look, it's very different. The nasal cavity is body temperature, 98.6 degrees, about 30 degrees higher than room temperature. Higher temperatures make things less viscous, thinner, not thicker as required by the patent.

Number two, on the tabletop, there is no dilution at all. The material, nothing is added to the material. In the nasal cavity, the nasal cavity secretes fluids all the time and they get mixed in with the material. And it would make it again thinner, less viscous, not thicker as the patent requires. And, moreover, in the nasal cavity, there are cilia. They beat a thousand times a minute -- a thousand times a minute. Their role is to share mucous and yank it back out of the nasal cavity. The body is producing constantly producing mucous. It has to be shared and moved. That same cilia action would make material that is thrown up the nose less viscous, not more

viscous as the patent requires.

You have to remember on the tabletop, you are just talking about still air. In the nasal passages, you are sniffing, sneezing, breathing, coughing. You are moving around. It's a more turbulent environment. So the notion that if it takes literally hours and days to return to setting viscosity on the tabletop, then in this environment, Barr's product would return to setting viscosity in the nose in only 30 minutes. There is no evidence, a complete absence of evidence on the in vivo recovery rate of Barr's product, complete absence of evidence.

Let me turn to obviousness, Your Honor.

Now, for our obviousness defense you are going to hear from Dr. Thomas Needham. He is a pharmaceutical formulator with 40 years of experience both in industry and teaching at the University of Rhode Island. This is what he does for a living. He is a pharmaceutical formulator and he is going to talk to you about the fact that the prior art renders these claimed nasal sprays obvious.

You will not hear from Aventis. You will not hear from a pharmaceutical formulator from Aventis to talk about the obviousness issues. Only Barr has brought a pharmaceutical formulator to the courtroom.

Now, just briefly for some context.

THE COURT: Counsel, bear with me just a moment.

MR. HURST: Take your time.

(Pause.)

THE COURT: Thank you, counsel. Go ahead. I should advise you that we're unable to detect where, going back to your earlier argument -- well, maybe you have found something that we haven't.

MR. HURST: And, you know, actually, I have to look at it, Your Honor.

THE COURT: Okay.

MR. HURST: Just to be totally clear, all I'm doing is our expert -- did we not have a lack of enablement?

MS. RURKA: It's right here.

MR. HURST: Yes.

THE COURT: Why don't you finish your thoughts and then return.

MR. HURST: Good idea, Your Honor. Thank you.

Now for obviousness. I just want to put a little context. I'm well familiar with the fact you know KSR, Your Honor.

THE COURT: Yes.

MR. HURST: I just want to identify one principle I think is important in this case from KSR. What the Supreme Court said is if there is a design need or market pressure to solve a problem and a finite number of identified, predictable solutions, the invention is likely

obvious. That is what they said. And that is the case here. There was a problem and a predictable solution. Here was the problem.

In the prior art, in the early 80s, nasal sprays were made with aerosols: CFC-propelled aerosols. CFCs, chloro -- I'm not even going to try. CFCs provide environmental problems and they were going to be banned. There was discussion of banning CFCs, and they were gradually being banned in various areas because they caused an environmental problem. So beginning in the late 80s, the pharmaceutical and other industries began searching for alternatives, and that included nasal sprays.

Schering Plough had a CFC-based aerosol: Vancenase. They converted to Vancenase AQ.

GlaxoSmithKline had Beconase, CFC-based, that they converted to Beconase AQ. And then they came up with an additional aqueous formulation, Flonase.

Aventis comes along and follows the same path, by now a well-worn path. They make Nasacort which was originally a CFC-based aerosol and they converted it to Nasacort AQ.

Now, why am I listing Nasacort AQ with a list of prior art products? It's because Nasacort AQ itself was in the prior art. And here is why. Those clinical trials that you heard about, the results were published on more than a

year before the application was filed. The results of those clinical trials informed people that there was an aqueous formation of TAA, that it worked, that it was given to 600 patients and the specific dosing that was used, that is in the prior art.

So why are we here? Aventis's argument, Your Honor, is that even though the product itself was reported in that literature, the ingredient list was not. The ingredient list was not. It was only the product itself. So they say our invention is the formulation. So the formulation is what makes our invention special. So the ingredient list they're saying wasn't public.

Well, Dr. Needham will explain to you that what an ordinarily skilled pharmaceutical formulator would do under these circumstances, if they wanted to make a TAA aqueous-based formulation as reported in the literature, all they would do is literally pick up the Physicians' Desk Reference and look up Vancenase and look up Beconase and see what their formulations were and just use their formulations. And, Your Honor, that is exactly what Aventis did.

Now, counsel spent a lot of time talking about Barr and Agis copying the Nasacort formulation. We're a generic drug company. We are a Congressionally-authorized encouraged industry. We, in fact, do copy brand products

when we believe -- when patents expire or we believe they're not legitimately protected by patents. That is what generic companies do. And we copy as closely as we can to get expedited FDA approval. So that's what we do.

But we are not the only party in this courtroom to copy a competitor's formulation. This was written by Aventis's inventor. As a starting point, he said, the qualitative formulation for Beconase AQ was used. And that is exactly what happened.

This is Nasacort in the left-hand column. That is Example 1 of the patent. And here are the three prior art formulations. They match up to the T, almost.

The top line, they're all glucocorticosteroids. To a pharmaceutical formulator, what that means is they have the same physiochemical properties and you can swap them out between formulations. So if you have a prior art formulation of that same drug category and you want to make TAA, you just swap out the TAA because you know it will work because it works with others in the same category. And that is exactly what Aventis did. You go right down the list and it matches up, matches up, matches up.

Here is one difference they're relying on. They say they switched out EDTA for phenylethyl alcohol. All right? So that is one of the things that they're saying, well, that is an invention.

Just a little context here. This benzalkonium chloride is a preservative. It keeps the bugs out of the juice. It kills the microbes. That is what phenylethyl alcohol is to do. They work together in tandem to make sure there is no microbes growing in the nasal spray. That is exactly what EDTA and phenylethyl alcohol do together. It's just a different preservative system. That is all it is.

And, in fact, when Aventis said this is our invention, we switched out EDTA for phenylethyl alcohol, we looked in the prior art. We picked up the Physicians' Desk Reference. And it is such a common preservative system, we found eight nasal sprays. We limited ourselves to nasal sprays. This combination is all over the Physicians' Desk Reference. But it's a really common combination for preservatives, EDTA with benzalkonium chloride. It's not an invention to use such a common preservative, especially when it's used in a bunch of other nasal sprays.

Now, to a pharmaceutical formulator, judge, this is really kind of basic stuff. You can pick what is called The Handbook of Pharmaceutical Excipients. And I know you have done a lot of Hatch-Waxman cases. Pharmaceutical formulators have this handbook in their offices. Any time they want to look up an ingredient and see its properties, they just pick it up. It's on the shelves. Dr. Needham has one, Dr. Donovan. Everybody has one. But plaintiffs'

expert on obviousness, he doesn't have a copy of the handbook because he doesn't do this for a living so it is not familiar to him maybe.

But if you look up benzalkonium chloride, it will tell you that you can use either phenylethyl alcohol or EDTA. Both are fine to create this preservative. If you look up EDTA, you will see right here, it tells you it's frequently used with benzalkonium chloride. So this is the difference in the formulation. And the handbook itself tells you, hey, here is one easy alternative.

Now, one of the things counsel said is, well, ours is odorless. EDTA is odorless and phenylethyl alcohol has an odor. That's true, it has a rose scent. How did they pick that? Why did they switch out to avoid the rose scent?

This is a quote from the inventor, Dr. Kim, who I understand will not be coming to testify, Your Honor. He says: Marketing suggested this. And there is nobody from Marketing listed on the patent. So the inventor, Dr. Kim writes a memo saying Marketing would like to eliminate phenylethyl alcohol, one of the two preservatives, because it has a distinctive or odor. And it does. It smells like a rose.

Now, is that an invention? Well, one point is both phenylethyl alcohol and EDTA are odorless under the

agreed construction which actually came from Aventis of odorless: odors which cause the user discomfort are absent.

Aventis is asking you to find that a rose scent -- phenylethyl alcohol is what makes a rose smell. Aventis is saying, Your Honor, that you should find that the rose scent causes users discomfort, which probably would shock the billion dollar rose industry in this country, I would think. A rose by any other name would smell as sweet. Shakespeare. So this has been a subtle issue for quite awhile.

Phenylethyl alcohol does not cause people discomfort as evidenced further by the fact that Flonase, which has this rose scent, has dominated the market, until it was genericized, from 1996 to 2006. So it apparently isn't causing users discomfort. Nasacort has never been higher than number three. So if it was causing people discomfort, it wouldn't be leading the market, I guess is my point.

Next, Aventis says, well, we have this special mixture of MCC and CMC. This is the suspension mixture that causes the viscosity. Well, here is what the claims says. The claims required a mixture of those two ingredients of about 85-to-95 percent MCC with the other 15 percent or 10 percent being CMC.

Now, all the other prior art has the same

mixture of ingredients and Aventis's argument is our mixture is special. Right? Because it gives this viscosity profile. The setting versus unsheared profile. That is the argument. So the first question is: Did Aventis invent that claimed ratio which produces the special viscosity profile?

Your Honor, they actually just purchased off-the-shelf products, literally. They wanted Nasacort to be thixotropic just like all the prior art formulations. And in order to get that ratio of CMC and MCC, they literally called FMC, a major pharmaceutical supply-house and said: Do you have a premixture for us? And FMC said, sure, we have two that might work, 591 and 611. Both of those pre-mixtures meet the claimed ratio. They both have 85-to-95 percent of MCC.

So then Aventis, Dr. Kim, tested up different formulations of both of those off-the-shelf products. And what they found is that both products actually gave this claimed viscosity profile that is set forth in the claims. They both did. They both did just fine.

Now, Aventis ultimately chose to use 611. Flonase we know in the prior art, they actually chose 591. So they chose a different one.

We tested Flonase. We tested the shear and setting viscosity. It matches up perfectly with the claims,

which agrees with Aventis prelitigation testing. That is what they found, too, when they used 591. But Aventis, when they tested Flonase, they said okay, it matches the setting viscosity but it has a higher shear viscosity. That is the argument.

This testing is subject to variability, batch-to-batch, the temperature in the room, how long you wait after you shear it to measure it. There is a thousand different things that can cause slightly different results. So this difference is immaterial.

To come up with a patent and say this is my distinction, this is the prior art, I claim a different shear viscosity, and that's my invention, well, the law, of course, is if you are going to work with a known prior art range, with a prior art range and you are just going to adjust the range, you have to come up with something new and unexpected. Something that gives you a difference in kind, not merely in degree. And absent that, it's not a valid patent.

That's the rule on obviousness.

So they say, well, I slightly adjusted this range. And they say it's going to give me something special. But their own testing showed it didn't give them anything special.

It is our position that Flonase and Nasacort,

they are exactly the same when they get sprayed up the nose. No difference at all. This is what their expert, he did this testing before the litigation, he said, you know, we did the testing, and what we found is that most regions showed quantitative deposition that was very similar between the two formulations, Nasacort and prior art Flonase, to the extent that the difference would be unlikely to be functionally detectable. Meaning if there is any difference, it won't mean any difference medically to the patients using these nasal sprays.

Even they didn't find that this special viscosity that they got from the off-the-shelf product made any difference.

By the way, they even said, no statistically significant difference. So there is really no difference at all between the prior art formulations and the current formations. It is really just cookie-cutter stuff, picking up the PDR and copying the formulation.

Last defense, anticipation, this is prior public use, which I know you know about. Just briefly for some context here. The law is pretty simple on this. Public use includes any use of the claimed invention by a person under the inventors who has no confidentiality obligation.

And the idea, obviously, is, if your invention is ready to the point where you are letting others use it

without a confidentiality obligation, a clock starts. You have got one year when you do that to get to the Patent Office, because they don't want you delaying. When it is ready and letting others use it, you have to get to the Patent Office so you don't artificially extend your patent monopoly. The later you go to the Patent Office the later your patent monopoly goes.

It doesn't matter whether the user knows anything about the product. All that matters is do they have a confidentiality obligation, and, number two, did they use it. So they could use this product in a closed room with the shades down and know its inner working for its ingredients and that would trigger anyway that one-year clock. That's the law.

There is a way around that, this experimental use exception, that only applies if that third-party use is necessary to prove that your product works, that it's a worthy product you can run to the Patent Office about. So they give you a kind of break, if you have to let third parties use your product to prove it will work and reduce it to practice.

That experimental use exception is no longer relevant in this case because of your ruling from Friday, Your Honor.

Here is why. It doesn't apply after reduction

to practice. Aventis throughout this case has asserted that they reduced this claim formulation to practice no later than May 1st, 1991. So did they go to the manufacturers when they did that? No. Instead, they ran a 600-person clinical trial. These folks had no confidentiality obligation. They could use the nasal spray at work, on the streets, at home, anywhere they wanted to.

As far as Aventis knew, these were pharmaceutical formulators in that group somewhere, or their brothers or sisters or parents were pharmaceutical formulators. They let it out into the public in huge amounts.

Here is when the clock started. December 19th, 1992, when they first let a person use their invention with no confidentiality obligation. And all they had to do if they really thought they had an invention with this formulation is get a patent application on file by December 19th, 1993, and then they would be fine. But they didn't do that.

They ran the clinical trials. And then they published them, they trumpeted these clinical trials in two different articles, and told the world we gave this product to 600 different people. Even then they didn't get to the Patent Office within a year. They waited the entire, over four years from reduction to practice until they went to the

Patent Office and filed a patent application.

When you are talking about 600 people with no confidentiality obligation, using a product, our view is that is the definition of prior public use, Your Honor.

Thank you for your attention.

THE COURT: Did you want to address the other defense?

MR. HURST: Yes. The lack of enablement goes from 348 of our pretrial order to, it goes many, many pages. In particular, if you look at Paragraph 353, we say, but the patent contains only one formulation example.

THE COURT: You are talking about 353 of your proposed findings?

MR. HURST: Yes, Your Honor.

THE COURT: The patent contains only formulas, for example, Nasacort AQ as described in Example 1, which does not reach the frontal sinus.

MR. HURST: Yes.

MR. BERGHOFF: That is the argument we agree is in the case, Your Honor. Clearly, the other one, about --

THE COURT: Would you go back to that other slide.

MR. BERGHOFF: -- is not.

THE COURT: That's what counsel is complaining about.

MR. HURST: This is the precise argument we are making. We are saying the only evidence that they suggest to show that they have taught a formulation that goes to the frontal sinus is in that Nasacort AQ. That is the point we are making.

So they haven't suggested anywhere that they have taught the full scope of the claims, as required for the enablement, under 112. That's the argument.

MR. BERGHOFF: May I put up -- can we turn the Elmo on? Is that possible?

THE COURT: Yes.

MR. BERGHOFF: This is just the agreed statement of contested issues of fact and law. C is the 112 section. And both of these are talking about depositing on all regions of the nasal cavity includes specifically the frontal sinuses.

That is what the issue is. That is what we fairly believed was the issue we were here to meet, not an argument that Nasacort is not a specific, the specific formula for Nasacort is not a specific enablement for the range of the claims on composition.

MR. HURST: I think counsel has misunderstood my argument.

No. This is all about frontal sinus.

All we are saying is, they didn't teach anyone

how to make any, any pharmaceutical formulation that reaches the frontal sinus. The point we were making in our pretrial order and the point I am trying to make now is the only example that they even say could reach the frontal sinus is only a sliver of the claims. And that doesn't teach the full scope of the claims. That is our position.

THE COURT: I understand. I think we are okay.

MR. BERGHOFF: If it is tied to the frontal sinus.

MR. HURST: It is totally tied to the frontal sinus. And I apologize if I didn't say that.

THE COURT: Let's get our first witness sworn.

... GEORGE GEORGES, having been duly sworn as a witness, was examined and testified as follows...

MR. HURST: Dr. Georges is testifying on noninfringement issues by agreement of the parties. We talked about the order of the trial in advance, infringement from Aventis, infringement and invalidity from Barr, and then the rebuttal from Aventis.

But there is traveling issues here. I hope this is not a concession that all of the witnesses can testify on validity issues. We are just making the accommodation for Dr. Georges' schedule.

THE COURT: That's fine.

DIRECT EXAMINATION

BY MR. BERGHOFF:

Q. Dr. Georges, could you please state your name?

A. George Georges. Same name, with an "s" at the end.

Q. Are you a medical doctor?

A. That's correct.

Q. Could you briefly describe your education for us?

A. Certainly. I have acquired my Bachelor degree in biology at the American University of Beirut in 1986. That was followed by an M.D. at the same university, School of Medicine. I emigrated to the United States in '91, and then completed a residency in internal medicine at the University Hospital in Cleveland, followed by a three-year fellowship in pulmonary and clinical care medicine at the University of Colorado. I passed my board certification in internal medicine, pulmonary medicine, as well as critical care medicine.

Q. Following your fellowship, what was your first position, Dr. George?

A. My first position was assistant medical director at a company in Collegeville, Pennsylvania, named Rhone-Poulenc Rorer, RPR.

Q. And that is a predecessor company to the plaintiffs in this case?

A. Yes. RPR history goes way back, through a series of mergers and acquisitions. It became known as Aventis, after

it merged with Hoechst Marian Roussel, late 1999, following that, through a merger of Aventis and Sanofi-Synthelabo, it became known as Sanofi-Aventis in 2004, late 2004.

Q. Could we put up what we have marked as Plaintiffs' Demonstrative Exhibit 205.

MR. BERGHOFF: Your Honor, I am sorry. With the first witness I always forget the booklet.

THE COURT: You may approach.

MR. BERGHOFF: Thank you, Your Honor.

BY MR. BERGHOFF:

Q. This is a demonstrative exhibit that you helped us prepare, Dr. Georges?

A. That's correct. That's the complicated genealogical tree of Sanofi-Aventis, as it is known today.

Q. We see RPR where you started towards the middle of the chart and Sanofi-Aventis near the bottom?

A. That's correct.

Q. As far as you know, is this an accurate representation of the corporate history?

A. Yes, sir.

MR. BERGHOFF: Your Honor, what is your pleasure on demonstrative exhibits, marking them?

THE COURT: No. We don't need to mark them. They are just that, demonstrative exhibits.

MR. BERGHOFF: Demonstrative exhibits, okay.

BY MR. BERGHOFF:

Q. **Dr. Georges, could you tell us about the positions that you have held at RPR starting in, I believe it was 1997?**

A. **Indeed. On August 1st, 1997, I joined RPR as an assistant medical director of respiratory U.S. in medical affairs. Then shortly after that, the following year, I was promoted to associate medical doctor in the same department.**

Then right following the merger of RPR and HMR to form Aventis, in April of 2000, I was promoted to medical director of respiratory in U.S. medical affairs.

I remained in that position until approximately mid-December of 2004, when, right, following the merger of Aventis with Synthelabo, I accepted a different position in the clinical operations outside the department, where I remained as a senior medical director from the middle of December 2004 until end of December of 2006.

And since October of 2006, I am back as a senior medical director of the respiratory, allergy and anti-infective in U.S. medical affairs at Sanofi-Aventis.

Q. **I assume you are familiar with Nasacort AQ, the product at issue in this case?**

A. **I am.**

Q. **What was your first involvement with Nasacort AQ?**

A. **I became involved in Nasacort AQ in 2000, when I**

became in charge of the respiratory department in the U.S. medical affairs division at Aventis.

Q. **How long did you remain in contact, in your job with Nasacort AQ?**

A. **Until middle of December 2004.**

Q. **How about today, Dr. Georges? Is Nasacort AQ part of your responsibility?**

A. **Yes. Beginning October 2006, I regained that responsibility, effective today.**

Q. **Briefly, what is Nasacort?**

A. **Nasacort AQ is a triamcinolone acetonide in an aqueous. It is formulated in the bottle. It is indicated for the treatment of symptoms of seasonal and personal allergy rhinitis in children 6 to 12 and adolescents 12 to 18 and in adults 18 and older.**

Q. **So if you are 6 and up, Nasacort AQ might be for you?**

A. **Correct.**

Q. **What type of product is it? Is it a suspension, a solution?**

A. **It is a suspension.**

Q. **Of what in what?**

A. **Many things. It is a suspension mainly of TAA, as we are referring to it now, in aqueous formulation. It does contain a number of preservatives. It is unscented. It has got thixotropic properties. It is formulated without phenyl**

ethyl alcohol, as you have summarized.

Q. Now, as medical director responsible for Nasacort AQ, did you have a group reporting to you?

A. Yes, I did. We started very small and we grew up to a relatively good sized group in early 2000. So I did have an individual who was full-time responsible for that product.

Q. And what were the responsibilities of you and your group with respect to Nasacort AQ in this time frame from 2000 to 2004?

A. My responsibilities spanned mainly three areas. One is being responsible for medical information about the product, as well as the accuracy of all medical data points and results concerning advertising and promotion. The last one, at least the design and implementation and publication of Phase 3B and Phase 4 clinical trials.

Q. The first item I think was medical information. For whom?

A. For anybody who asked questions on Nasacort AQ, mostly health care providers.

Q. And advertising materials, you have reviewed those before they went out the door?

A. That's correct.

Q. And then we will talk a little bit about Phase 4 clinical trials.

What is a Phase 4 clinical trial?

A. **A Phase 4 clinical trial is clinical trials that are conducted post-approval and while the drug is being marketed. They are mainly indented to further correct the efficacy, safety, as well as additional outcomes on a particular product.**

Q. **Were there any Phase 4 clinical trials for Phase 4?**

A. **There were indeed many Phase 4 clinical trials conducted.**

Q. **Can you give us a rough estimate of the number?**

A. **It would be around, between ten to 20 in that period.**

Q. **What were the purposes of these Phase 4 clinical trials for Nasacort AQ?**

A. **As I said, various things. Furthering the understanding of comparative efficacy versus existing products of similar class, as well as furthering the understanding of the safety of this product using innovative or novel measures of safety. Looking at different shading factors, such as sensory attributes, quality of life, patient preference, projected compliance with the product, things like that.**

Q. **Let's focus on the sensory attributes. Describe what that might be, a Phase 4 clinical trial on sensory attributes?**

A. **Yes. That is a trial that is aimed at investigating the patient's perception of the product's sensory attributes**

when it's sprayed in their nose. That's something I could come up with.

Q. That's fine. Do these studies just involve Nasacort AQ or were there other products that were involved?

A. There were other products involved. Those were comparative studies, comparing Nasacort AQ to other similar products in the market.

Q. What were some of those products that were compared for the sensory attributes, the patient perception?

A. We compared Nasacort AQ to Beconase AQ, to Flonase, as well as to Nasonex.

Q. Was it common in the industry, as far as you know, to conduct Phase 4 clinical studies at this time on sensory attributes, patient perception of sensory attributes?

A. I believe we were the first to sort of pave that road, in terms of research, because, obviously, these type of compounds were all, became available in the late eighties, mid-nineties. So there was very little known about that topic, as concerning enter intranasal steroids.

So I think we started doing that type of study to better understand the differentiation between Nasacort AQ and other compounds .

With this particular class of products, it's extremely difficult to differentiate based on mere efficacy outcomes or safety outcomes.

Numerous studies have been conducted that showed that the efficacy and the safety of these compounds are very similar, very close.

So we were trying to identify different aspects of differentiation for Nasacort AQ. And we decided, based on the profile, that that is something that patients may be able to perceive as different. And that's why we conducted these studies.

Q. **What sensory attributes did these Phase 4 clinical trials look at?**

A. **We looked at taste, aftertaste, strength of taste, liking of taste, same thing for odor, strength of odor, liking of odor. We looked at amount of runoff. We looked at overall like. We looked at moistness feeling. And we looked at a projected patient preference based on the overall liking of the sensory attributes.**

Q. **What is Nasacort AQ's property with respect to odor?**

A. **With respect to odor, as the package insert states, it is unscented.**

Q. **As far as you know, was it the first unscented aqueous intranasal spray?**

A. **As far as I know, it was the first.**

Q. **What makes it unscented? Why is it unscented?**

A. **I believe it's the absence of phenyl ethyl alcohol, which inherently smells like rose petals.**

Q. **You were here, I think, for Barr's counsel's opening statement about how sweet a rose smells. Why could that be an issue?**

A. **I do buy roses for my wife on all the occasions. I know she likes them. I think some people enjoy the smell of fragrance or perfumes. And other people just don't.**

It is a matter of preference. Some people prefer certain scents over other scents. Some prefer no scent over scent. That is where we are.

Q. **The removal of phenyl ethyl alcohol in the Nasacort QT formulation, did that have any other benefits related to patient sensory attributes?**

MR. HURST: Objection, Your Honor. The witness is beginning to testify as if he is an expert. We didn't have an expert report from Dr. Georges. He was not actually offered as one.

THE COURT: I will sustain the objection.

MR. BERGHOFF: That was probably an inartful question. I do mean to ask him to describe these Phase 4 clinical trials that he was in charge of. Let me try again, Your Honor.

BY MR. BERGHOFF:

Q. **Does the absence, as far as you know, in your knowledge of Nasacort AQ, from having coordinated the Phase 4 clinical trials, is there any connection between the**

absence of phenyl ethyl alcohol and any of the other sensory attributes that you had part of the, directed in part of the Phase 4 clinical trials?

MR. HURST: Same objection, Your Honor.

THE COURT: You don't believe this is venturing off into the area of expert testimony?

MR. BERGHOFF: No, Your Honor. This is his own personal knowledge of these Phase 4 clinical trials. He is a medical doctor.

MR. HURST: He is now testifying about his interpretation of data from Phase 4 clinical trials. We actually asked him about this at his deposition, and he answered mostly that he is not an expert in this area.

THE COURT: I won't let him do what counsel has just described he believes he is doing. With that proviso, why don't you rephrase your question.

BY MR. BERGHOFF:

Q. **Do you have an understanding of the connection of the absence of phenyl ethyl alcohol from Nasacort AQ and any other properties of Nasacort AQ?**

A. **Based on what I read in the literature, that scent is essentially phenyl ethyl alcohol. That is public knowledge. That is published literature.**

Q. **Did the results of the Phase 4 clinical trials that you have discussed that you were responsible for while**

medical director, were they published in medical journals?
A. Yes.
Q. How many publications?
A. About six or seven publications.
MR. BERGHOFF: Your Honor, these are in evidence. I am certainly not going to walk Dr. Georges through all of them. I did want to just put one up on the screen.
THE COURT: Okay.
BY MR. BERGHOFF:
Q. If we could look at Plaintiffs' Trial Exhibit 409. The second page, is this one of the publications of a Phase 4 clinical trial on sensory attributes?
A. Yes.
Q. What is the subject of this publication?
A. The objective was to compare patient assessments of sensory attributes of three intranasal corticosteroid sprays, TAA, FP, and MR, which is Nasacort AQ, Flonase and Nasonex.
Q. What was Aventis's role in connection with this study?
A. We provided funding, as well as input to the protocol and publication.
Q. Did Aventis or Sanofi-Aventis actually conduct the study?
A. No. The study was conducted by investigators in three

countries, in Norway, Germany, and Switzerland.
Q. What journal was this published in?
A. The Annals of Allergy, Asthma, and Immunology.
Q. What type of journal is that?
A. It's a peer-reviewed journal.
Q. Respected?
A. Yes. Widely read by allergists and people interested in that field.
Q. Could we just look at the -- could we actually go to the results and conclusion section on the first page.
Is it your understanding, Dr. Georges, that this paper describes the results of this particular Phase 4 clinical study, comparing Nasacort AQ to competitive products?
A. It describes at least some of the results, yes.
Q. And what is your understanding of the results of the study?
MR. HURST: Objection, Your Honor. This is obviously expert testimony.
THE COURT: Overruled. Go ahead.
THE WITNESS: Could you repeat the question?
BY MR. BERGHOFF:
Q. What is your understanding of the results of this particular Phase 4 clinical study?
A. My understanding is exactly as they read. The results

report that the TAA was rated as having significantly better comfort during administration, less irritation, less odor strength, preferred odor, more moistness of nose and throat, a moderate taste, it had a P value that was statistically significant, it also had a preferred taste. That is in comparison to Nasonex.

And there is another paragraph comparing it to Flonase that also shows that it was rated as having less odor strength, preferred odor, more moistness of nose and throat, a moderate taste versus Flonase.

That was immediately following administration.

Then there are results reported two minutes after administration that comment that TAA was rated as having less aftertaste than Flonase or Nasonex.

Q. Do you have any understanding of the results of this particular study with respect to patient preference or compliance?

A. The questionnaire used in this study queried patients about their projected compliance based on their answers. And more patients indicated that they would be more compliant with treatment if given a prescription of TAA, or of Nasacort AQ, at about 67.4 percent than if given a prescription with Flonase about at 55 percent, or Nasonex at 50 percent.

Q. Thank you. Could I ask you to turn in your book,

perhaps we could put up on the screen the first page of Plaintiffs' Trial Exhibit 313.

Do you recognize this document, or at least set of pages?

A. Yes.

Q. What is it?

A. It's a, I think it's a booklet that summarizes the product attributes of Nasacort AQ as it pertains to its efficacy, profile, it's safety and tolerability, as well as patient preference and compliance review.

There is also full prescribing information included here, as well as letters to, a sample of a letter to physicians as well as to patients from a managed care organization.

Q. Is this, or am I wrong, is this advertising material related to Nasacort AQ?

A. It would be considered as such, yes.

Q. And is this something that your group would have reviewed for accuracy between 2002 and 2004?

A. Yes, sir.

Q. What was the purpose, when your group reviewed advertising materials, what was the purpose of the review?

A. Our goal as medical reviewer of advertising and promotion is to ensure the medical accuracy, relevance, and fair balances of the information provided.

Q. **Could you turn to -- I am sorry, these pages are not numbered in a convenient fashion. It's just the Bates numbers. The last three digits are 920. Maybe we can put it on the screen.**

It's a little further in.

THE COURT: Perhaps this would be a good time -- we are close to the time I need to pause. We will resume at 2:00.

(Luncheon recess taken.)

THE COURT: Please be seated.

You may proceed.

BY MR. BERGHOFF:

Q. **Dr. Georges, I believe we left off, we had PTX-313 up on the screen. And just to reorient us, is this an example of advertising material for Nasacort AQ that you and your group reviewed in the time period between 2000 and 2004?**

A. **Yes.**

Q. **And were materials like this, did they ever get to the FDA?**

A. **Yes, we submit all advertising and promotional material to DDMAC, which is a division of FDA.**

MR. BERGHOFF: Okay. We have up on the screen, Page 920, and if we could just look at the section from "favorably," what is the word there, "favorably rated," down to "no fragrance?" Eric, if we could pull that up? A

little higher. There we go.
BY MR. BERGHOFF:
Q. What does this portion of the advertising material state, Dr. Georges?
A. It states: Favorably rated by patients on the basis of odor, taste and overall comfort.
And it cites two references, number four and five, which four is the Bachert study that you showed earlier and five is the study by Dr. Gerson and colleagues in the Journal Sensory Studies.
Q. And those are both publications of phase IV clinical trials?
A. Yes.
Q. What else does this advertising material state?
A. It says: More patients would definitely comply with a prescription for Nasacort AQ, at 67.4 percent. Then for Flonase, 55 percent, or Nasonex at 50 percent. And that is a direct pickup from the Bachert publication that you showed earlier.
Q. And the last two points for us, Dr. Georges?
A. There is one that says no irritating alcohol. And there is one that says no fragrance or unpleasant taste.
Q. And what is the reference to no irritating alcohol refer to in this advertisement?
A. I believe that is from the package insert. We don't

have, there is no alcohol in the formulation of Nasacort AQ.

Q. **And who is the intended audience for this particular page in this exhibit?**

A. **It's mostly healthcare professionals. So it's professionals.**

Q. **Physicians?**

A. **Physicians, nurses.**

Q. **And let's just turn to the Page 929. Is this also advertising material for Nasacort that your group reviewed?**

A. **Yes.**

Q. **And who is the intended audience for this particular page?**

A. **My understanding is organization patients, so patients belonging to managed care or covered by managed care organizations.**

Q. **Would that be an HMO?**

A. **You can refer it to as such, yes.**

Q. **And there is a sentence highlighted on the page. What does this convey in this advertising piece?**

A. **It reads: In addition, Nasacort AQ has no unpleasant taste, no fragrance and no irritating alcohol.**

This is a description of the sensory attributes of Nasacort AQ taken from the results of the studies in Bachert as well as the package insert.

Q. **Thank you.**

MR. BERGHOFF: No further questions, Your Honor.

THE COURT: Counsel, you may cross-examination.

MR. HURST: Thank you, Your Honor.

THE COURT: Counsel, for your convenience, I meant to mention this earlier, you can turn the lectern.

MR. HURST: This works fine.

CROSS-EXAMINATION

BY MR. HURST:

Q. **Dr. Georges, we haven't met before. My name is James Hurst, and I represent Barr Laboratories.**

A. **Good afternoon.**

Q. **I just want to ask you a few questions about the patient preference studies that you testified about. These were studies designed to help support marketing claims. Correct?**

A. **They are designed to understand the attributes of the product as it compares to Flonase and Nasacort and Beconase.**

Q. **And they were actually, though, designed to help or at least they were used -- will you agree they were actually used to support marketing claims?**

A. **That's correct.**

Q. **Okay. And these patient preference studies that you talked about, they were sponsored by Aventis. Correct?**

A. **That's correct.**

Q. **And the protocols in terms of deciding what questions**

to ask and how to ask the questions to compare Flonase versus Aventis, that was also something Aventis itself participated in doing. Correct?

A. The questionnaires were developed jointly by Dr. Bachert and Aventis.

Q. But Aventis had a role in deciding how to ask the questions in terms of comparing patient preferences for Nasacort versus Flonase. Correct?

A. We did input into the protocol, if that is what you are asking, yes.

Q. And why don't we take a look at Plaintiffs' Exhibit 409. This is one of the documents you talked about with counsel. Correct?

A. Yes.

MR. HURST: If you take a look at the second page. Why don't you highlight the names, if you could, for me of the two authors.

BY MR. HURST:

Q. The senior author there, he actually is an Aventis employee. Correct?

A. You mean the first or the second?

Q. Dr. El-Akkad, he is Aventis employee. Correct?

A. Correct.

Q. So an Aventis employee played a role in developing the protocols for this comparison with respect to patient

preferences. Correct?
A. That's right.
Q. Now, I would like to show you some advertising that Aventis actually used or cited these. You looked at some yourself with counsel. Right? Some of the advertising that cites these studies that Aventis conducted?
A. Yes.
MR. HURST: I would like to take a look at Defendant's Exhibit 114.
BY MR. HURST:
Q. And you recognize this is a Nasacort advertisement?
A. Yes.
MR. HURST: Take a look at the second page.
MR. BERGHOFF: Your Honor, I don't know what protocol would be. Do you have a copy?
MR. HURST: I'm sorry.
MR. BERGHOFF: No, no. That's fine. That's fine.
THE COURT: You haven't seen this?
MR. BERGHOFF: I won't represent I have never seen it.
MR. HURST: Yes.
THE COURT: That would be the protocol.
MR. HURST: Yes. I apologize, Your Honor.
May I approach, Your Honor, the witness?

THE COURT: Yes, you may approach freely.

MR. HURST: Is it protocol to ask permission for each approach?

THE COURT: No. Once you ask for the witness, you have leave to approach the witness freely.

MR. HURST: Thank you, Your Honor.

And if I can hand up for Your Honor?

THE COURT: Sure.

(Documents passed forward.)

BY MR. HURST:

Q. **Okay. You recognize this is an advertisement for Nasacort?**

A. **Yes.**

MR. HURST: If you go to the second page.

BY MR. HURST:

Q. **You will see at the top, it says preferred by twice as many patients over Flonase and Nasonex. Do you see that?**

A. **Yes.**

Q. **And there is a footnote, and if you can just check, that actually cites one of Aventis's patient preference studies. Right? It's the last page.**

A. **Yes, it's the Bachert study.**

Q. **And that study was also a study that Dr. Akkad from Aventis. He was the senior author on the paper?**

A. **El-Akkad, yes.**

Q. **El-Akkad. My apologies. Now, what this advertisement says is that patients preferred by, preferred by twice -- strike that. Nasacort is preferred by twice as many patients over Flonase and Nasonex. Right?**

A. **Yes.**

Q. **But in terms of their purchasing decisions, that didn't really bear out, did it?**

A. **I'm not sure I understand the purchasing decision.**

Q. **In fact, Flonase, until it was genericized, had approximately three times the sales of Nasacort. Right?**

A. **I'm not in sales and marketing so I don't know the exact figures. I guess Flonase was the market leader at that time.**

Q. **Does that sound about right? About three times the sales, that neighborhood?**

A. **I don't know the exact figures.**

Q. **Would you agree with respect to purchasing decisions, more patients seemed to prefer Flonase than Nasacort with respect to purchasing decision?**

A. **I don't know if purchasing is based on preference or based on -- it could be based on the fact that their doctors are prescribing them that product so it's not strictly decided by patient preference. It's what the doctor prescribes.**

Q. **So it might be a patient preference and a doctor**

preference leading to the higher sales for Flonase?

A. **It could be both.**

Q. **Okay. Now, I'd like to turn to the last page. Actually, can we do this? You were here for opening statements. Correct?**

A. **Yes.**

Q. **And did you hear counsel for Aventis talk about these clinical studies that were conducted in 1993 and 1994?**

A. **Yes.**

Q. **And counsel for Aventis indicated that they were not run for any commercial purpose. Did you hear that?**

A. **I recall, yes.**

Q. **But, in fact, those two clinical studies from 1993 and 1994 were in fact used to support marketing claims. Isn't that true?**

A. **Which studies are you referring to exactly?**

Q. **The Settipane study and the Kobayashi study?**

A. **Those are studies that eventually used to support marketing claims.**

Q. **And here if you take a look at Defendant's Exhibit 114 at Page 5, at the top there, you will see it provides fast effective first-day nasal allergy relief. Do you see that?**

A. **Yes.**

Q. **And if you take a look at the footnote to that, on the very last page, 009, if you highlight the footnotes 2 and 3,**

you understand these are the two studies that I and your Aventis counsel discussed in connection with this public use defense that we were talking about. Right?

A. Yes.

MR. HURST: I have no further questions.

THE COURT: Redirect, counsel.

MR. BERGHOFF: Yes, one point.

REDIRECT EXAMINATION

BY MR. BERGHOFF:

Q. Do you still have the exhibit counsel handed you in front of you? Can you tell us its date and perhaps from the references cited? It would be the last page. I'm sorry, Dr. Georges. I should have been clearer.

A. Can you tell me the date of the advertisement, please?

Q. Yes.

A. I don't see it readily.

Q. Is it at least some time after 2002? What is the date of the Bachert study?

A. Yes. It has to be after the date of the most recent reference, so I would assume it is after August 2002.

Q. And you were not in charge of reviewing advertising materials as of 2002 for Nasacort?

A. I had a direct report that was a full-time job that was on this product. I wasn't the primary person.

MR. BERGHOFF: No further questions.

THE COURT: Thank you, sir.

THE WITNESS: Thank you, all.

MR. BERGHOFF: Mr. Rich will handle our next witness, Your Honor.

THE COURT: All right.

MR. RICH: I will call Dr. Michael Kaliner.

- - -

PLAINTIFFS' TESTIMONY

... DR. MICHAEL KALINER, having been placed under oath at 2:15 p.m. as a witness, was examined and testified as follows ....

- - -

MR. RICH: Your Honor, may I approach the witness?

THE COURT: You may.

(Documents passed forward.)

DIRECT EXAMINATION

BY MR. RICH:

Q. **Dr. Kaliner, can you tell us your full name?**

A. **Michael Allen Kaliner.**

Q. **And I know you know these answers pretty much by heart but the rest of us could use looking at your CV. If you could pull that up. What is your educational background, Dr. Kaliner?**

A. **I started college at Duke for a year; then transferred**

to the University of Maryland, where I graduated with a BS; and then I got my medical degree at the University of Maryland.

Q. And after you completed your MD, did you do any further training in medicine.

A. Yes. I did internal medicine, finishing at the University of California at San Francisco; and then did my allergy training at Harvard Hospital in Boston.

Q. What is your primary practice?

A. I'm trained in both internal medicine but I practice primarily in allergy and immunology.

Q. Are you board certified in anything?

A. I am board certified in internal medicine and allergy and immunology.

Q. Have you had any other relationship with the Board for Allergy and Asthma?

A. I have had the opportunity to serve on the Board of Allergy and Immunology, which is the board that certifies physicians trained in allergy as to whether they can be then certified in allergy.

So we regulated all those processes. And I was chairman of the board in 1986 to '87.

Q. Over the course of your career, how many patients have you treated for allergies?

A. It's a hard number to come up with, but 10 to 20,000.

Q. **Would you characterize those patients in any way among the allergy group?**

A. **I am, as Dr. Meltzer will be, I am an allergist's allergist. I get the referral of all the difficult cases in the Washington area from allergy, ENT, and primary care doctors.**

Q. **Would it be fair to say through your treatment of patients that you have become familiar with intranasal steroid sprays?**

A. **Yes, I am very familiar where intranasal steroids.**

Q. **What are the intranasal steroid sprays you are prescribing today?**

A. **Today I am still prescribing Nasacort AQ and Nasonex. Those are the primary ones I use. But there others on the market.**

Q. **One we have heard about is Nasonex and studies of Nasonex. Has Nasonex always had the same formulation?**

A. **No. Nasonex was formulated with a phenyl ethyl alcohol and had a smell to it. So they reformulated to get rid of that smell about four or five years ago.**

Q. **Where do you practice today?**

A. **I have a state-of-the-art center in, near Washington, D.C. One office is in Chevy Chase and one is in Wheaton, Maryland.**

Q. **I would like to go back to the start of your career**

now to give some background in terms of your practice. After your fellowship, where did you begin practicing?

A. After I finished my fellowship, I was in the military at the time of Vietnam, and so I served two years in the Air Force. And then when I finished the Air Force, I went to the National Institutes of Health and continued my training and research there.

Q. Looking at that page of your CV, the entries for the National Institutes of Health, it discusses NIAND. What is that?

A. The NIH is a consortium of institutes, one of them is the National Institutes of Allergy and Infectious Diseases, which is where allergy, immunology and all the infectious diseases are studied. That is where I was housed. I was the head of the allergic diseases section, which meant that I was directly responsible for allergy research for the NIH.

Q. Did you have any responsibility for training or patient care at NIAID?

A. I ran the allergy training program for 18 years, and trained approximately a hundred fellows that were practicing mainly in the United States and worldwide.

Q. And I think you said you had some responsibilities relating to a laboratory at NIAID?

A. Well, I was head of a laboratory where we had anywhere from 10 to 30 people who would work with me, doing research.

And I also was the director of the outpatient program at the NIH, where I was responsible for the research done, the clinical research done within the NIAID, not just allergy but infectious disease as well.

Q. **As part of your work at NIH, did you consult with any governmental agencies?**

A. **Yes, I consulted regularly with Health and Human Services and Walter Reed. And anything dealing with allergy and immunology, they came to me.**

Q. **Back to today, do you have any academic appointments?**

A. **Yes. I am currently professor at George Washington University Medical School. I actually direct the training program at the Washington Hospital Center, which is the largest hospital in Washington.**

Q. **In your career, have you been involved with any professional organizations?**

A. **I was fortunate enough to be part of the American Academy of Allergy, Asthma and Immunology, which is the largest professional society of allergists in the United States, and I was fortunate enough to be president ten years ago. And then subsequently, I have gotten associated with the World Allergy Organization, which is a federation of allergy societies, and there are 74 societies, 35,000 members, and I am the immediate past president.**

Q. **I know you talked about your service at the Air Force**

Base, Keesler Air Force Base. Did you perform any other military service?

A. **When I came to the NIH, I was in the Public Health Service, and I spent 10 years in the military. I retired in '93 as an 06.**

Q. **Have you authored any publications on allergy and asthma topics?**

A. **I have published about 500 articles, manuscripts, reviews, journals, in my career.**

Q. **Those are listed in your CV?**

A. **They are in my CV.**

Q. **We won't walk through them one by one.**

Have you been involved in any clinical trials?

A. **We did clinical trials at the NIH within protocols. So they were restricted trials. We had to actually have approval for trials we created ourselves. But when we set up the Institute for Asthma and Allergy, which is where I currently work, it was set up as a state-of-the-art referral center for very difficult patients, which is who I see all the time.**

But we also set aside a part of our practice for research. And about 30 percent of our resources are devoted to research. And we do somewhere between 16 and 30 studies a year, and in total have done about 500 clinical trials.

Q. **Have you invented anything related to allergy or**

asthma?
A. I have a couple of patents, yes.
MR. RICH: At this point, Your Honor, we would like to submit that Dr. Kaliner is qualified as an expert in allergy, nasal anatomy and physiology.
MR. GRACEY: No objection.
THE COURT: He is accepted as such.
BY MR. RICH:
Q. I would like to turn to the substance of your testimony. We have a diagram of the nose.
You have a laser pointer with you that will hopefully HELP to walk through this. Can you tell me how air enters the nose?
A. When you breathe in, air comes in through the vestibule right here, the nares. And that goes through this vestibule, and then goes on a flow back to the pharynx, and then it's breathed into the lungs.
Q. In terms of the vestibule, what kind of cells form the surface of the vestibule?
A. Well, the outer surface of the body is covered with a squamous epithelium on which there is a carotin layer. When it gets to the nose, the squamous epithelium persists inside the vestibule. Right at the valve right here, there is a transition from the skin's epithelium, the squamous, to the pseudo-stratified epithelium that makes up the mucous

membranes.

Q. Are there cilia on the cells that are in the nasal vestibule?

A. No, squamous cells are non-ciliated.

Q. Are there any other structures that would help trap or prevent the flow of --

A. Well, there is hairs, depending on who you are, lots of them. And that traps air as it goes through, it helps filter.

Q. There is a label there for the nasal valve. What is the nasal valve?

A. That is the narrowest part of the nose. So air comes in in a stream, and it is narrowed down at this juncture, and then spreads out and comes into the nose, where it then flows. We can talk about the flow. I think we have another diagram that might do better than this one.

Q. We will turn to another diagram.

A. When you breathe in, the idea is to get the air to the pharynx. But you want air to be cleaned of everything that is removable, all particles. It needs to be at body temperature and fully humidified with water. In a tenth of a second it takes to go from here to here, because of the way the nose works, this air is clean, humidified and filtered and warmed.

What happens is the air hits the turbinates,

these inferior and middle turbinates, and then swirls in here, and then as it comes to the back of the turbinates it becomes laminar and flows to the lungs.

There is a second process I wanted to mention, as long as the slide is here. That is sniffing. If you just focus, everybody here focuses on breathing through your nose, you can feel the air flows this way. When you sniff, you are actually directing air directly up to where the olfactory epithelium is here, so it is a whole different direction of flow when you sniff versus when you breathe. And I will come back to that later.

Q. I have one more question with regard to before the nasal valve. Particles that are deposited before the nasal valve, are they cleared to the back of the throat?

A. I don't think so. I think the valve is outflow and beyond the valve is inflow.

Q. So they are cleared forward in some manner?

A. Right.

Q. If we could go back to the previous diagram, just to get an idea of the overall structure of the nose.

What are the boundaries of the nasal cavity?

A. Well, the top is the kalvarium, the bottom of the brain. And the bottom is the hard pallet, top of the mouth. Posterially, it is the pharynx. In the front would be the nose, the outer structure of the nose. Laterally would be

the turbinates, and the lateral wall of the sinuses, which you can't see in this cutaway picture, there is a septum that separates left and right.

Q. You mentioned the turbinates. I think you testified earlier that they make the air turbulent?

A. That's correct. These are console-shaped, C-shaped bones here, here and here. And their purpose, at least in part, is to make the air turbulent, which is why they are named turbinates, and they occupy a fair amount of space in the nose. But they also serve the purpose of secreting mucous and protecting the structures underneath of them.

Q. What are the spaces between the turbinates called?

A. So this space right here between the -- underneath the inferior turbinate would be the inferior meatus, this space here would be the middle meatus, you have to kind of curl your hand underneath that to get to that. Here is the superior meatus.

Q. We have another diagram that would show this a little more easily. You can tell me if it is clear. Which meatus does most of the airflow through the nose go?

A. This is a picture as we look in the nose with an anterior otoscope, spreading the nose and then looking inside. What you see is the nasal septum on this left side here and the inferior turbinate, which is the largest of the turbinates. And it blocks 40 percent, give or take, of the

nasal passage. And then behind it and also at a 45-degree angle is the middle turbinate, often looking at a slightly different color. Between them they take about 50 percent of the open space, so air has to hit these two turbinates as it flows into the nose. And that's why they are so effective.

Q. **I guess I wasn't quite clear. Between which turbinates or which surfaces does air flow through the nose?**

A. **When you breathe it in, it's going to impact on the anterior aspects of these turbinates, but it will hit all the surface of the turbinates.**

Q. **Can you tell me, first of all, what this slide depicts?**

A. **It's the same as the first picture, except the inferior and middle turbinates have been removed so you could see what's underneath of them. This is the nasolacrimal duct, which is why your nose runs if you cry, because tears come through here. So that's under the inferior turbinate. Under the middle turbinate is this groove, this semi-linear hiatus, into which the frontal sinus recess drains. So the frontal sinus actually comes right down to this spot right at the anterior aspect of the middle turbinate.**

This area right in here is the maxillary sinus and the drainage is right there. And then these are ethmoid sinus ostea.

Q. **You talked about the, I guess, four different sinuses. Can you show us where the sinuses are located?**

A. **Well, they are around the eyes. And so the sinuses are hollowed cavities in the skull around the eyes. So in your cheeks is the maxillary sinus. Then above the eye is the frontal sinus. Between the eye is the ethmoid sinus. Behind the eyes the sphenoid sinus. Here is the sphenoid and here is the frontal. You can't see it because they are closed with bone. But the maxillary would be right here and the ethnoid air cells would be right along here.**

Q. **This diagram shows a problem to the frontal sinus?**

A. **Right.**

Q. **It looks like a less complex route to the frontal sinus than the statements and the slides in the opening from Barr. Do you have any reason to believe that this diagram is incorrect?**

A. **No. I mean, I don't have any reason to think that the frontal sinus drainage is all that complex. It is a recess right through here, it is relatively close. It's assisted by gravity. And clinically, I take care of literally tens of thousands of patients with difficult-to-manage sinus disease. Yes, we do have some patients with frontal disease. But relatively speaking, we see far more people with ethmoid and maxillary sinus than we see with frontal sinus disease.**

So they must be able to communicate pretty easily when the other sinuses have problems.

Q. Just to be clear, do you believe that airflow reaches the frontal sinus?

MR. GRACEY: Objection, Your Honor. This is beyond the scope of Dr. Kaliner's opening expert report.

MR. RICH: Your Honor, it is not beyond the scope. He first submitted to talk about anatomy. His report talks about the anatomy. In fact, it talks about the anatomy of the pathway to the frontal sinus.

MR. GRACEY: Your Honor, Dr. Kaliner's opening expert report does not talk about airflow into the frontal sinus.

THE COURT: Let's see counsel at sidebar.

(The following took place at sidebar.)

THE COURT: Why don't you point out where you say it does talk about the issue at hand.

MR. RICH: Your Honor, he said he would talk about the peri-nasal sinuses. This was an opening report. The rebuttal to his report wasn't served until the next round. We weren't entitled to a third round of reports. Dr. MacKay, who was talking about --

THE COURT: Is there a report that has not been objected to?

MR. RICH: There are so few reports that haven't

been objected to. This exact language is in a report that hasn't been objected to.

MR. GRACEY: Your Honor, if I may, they have the burden on infringement. If he was going to opine on Barr's product Nasacort in the frontal sinus, it should have been in the opening report. If he wants to respond to Dr. MacKay's statement on this in the rebuttal case, that is fine.

THE COURT: I will sustain that objection.

(End of sidebar conference.)

BY MR. RICH:

Q. Back to anatomy, I would like to ask about the point where it says opening to maxillary sinus. Can you tell me if that opening in your expert opinion is more or less accessible than the opening to the frontal sinus?

A. I think it's less accessible. It is very, within a semi-linear hiatus underneath what is oftentimes a very large swelling of this ethmoid bullous, which is often quite large. And its tucked underneath what's missing here, the middle turbinate.

So I think it's less accessible than this anterior aspect of the middle meatus, which has direct airflow that would impact on I would think every breath.

Q. Now, I would like to look at the entire nose. What is the covering of the nasal cavity once you get past the nasal

valve?
A. It's a pseudo-stratified polymer epithelium with cilia.
Q. We have a diagram here. Can you point out to me what the cells on the surface are and the various features of this diagram?
A. So this is, in contrast to the squamous epithelium, which is flattened cells, these are elongated epithelial cells, each of which has on the surface a number of cilia. Then interspersed amongst the epithelial cells are goblet cells that contribute to the mucous blanket. And there is a copious amount of submucous glands, and I think I will show you a picture in a moment, that gives you an idea how thickly endowed the mucous membranes are with submucous glands that produce the majority of the mucous.
Q. Is the mucous on the top layer of the nasal mucosa?
A. It is not as simple as it looks. The cilia are tiny hair-like fibers that beat, they beat in an aqueous layer. This is called the peri-ciliary layer, it is actually aqueous. Then the mucous, which is a mucopolysaccharide, floats on the surface of this aqueous layer, and moves caudet, towards your pharynx.
THE COURT: Moves what?
THE WITNESS: Moves back, caudet, it's back.
BY MR. RICH:

Q. **How big is the aqueous layer?**

A. **Well, we have measured it. It is only a couple hundred microliters for the entire nose, because this is a very thin layer of cilia. It is a very thin, widespread, totally spread layer.**

Q. **What, in terms of this diagram, is cleared through mucociliary clearance?**

A. **Right. This mucous blanket is constantly moving from the front of the turbinate to the back of the pharynx.**

The amazing thing is you are producing two quarts of mucous a day. So you're constantly swallowing this mucous blanket. You are just not aware of it. And things that are trapped, everything that is particulate is trapped, stopped in those, it goes on the mucous blanket, is swept in the pharynx, swallowed, and destroyed by acid and hydrolysis in the stomach.

You are swallowing all day long. The aqueous layer is quite different, though.

This is a post-events layer. When you impregnate this with lots of molecules to keep you from getting infected with bacteria, and has iGG and iGA in it, it is rather stagnant. So this does not move at all. It is just the mucous blanket that moves.

Q. **One of the things we heard during Barr's opening is that the cilia shear the mucous. To your knowledge, does**

that occur?
A. Well, I am going to say that I don't know what he means by shear the mucous. But the answer is no. What happens to this mucous, it is intact and it goes from front to back. The bottom layer is moved by the very tip of the cilia touching the bottom of the mucous and it just moves the blanket back.
Q. What is the mucous made of?
A. It is a mixture of things. The mucous itself is a mucopolysaccharide. There are a lot of things imbedded within the mucous, including trapped marker molecules. It is a complex mixture. We identified 15 or 20 different components to it.
Q. Is the mucous hydrophilic or hydrophobic?
MR. GRACEY: I'll object. That again is beyond the scope of his opening expert report.
THE COURT: Are you saying this area?
MR. RICH: We can discuss it later. It won't change in the meantime.
THE COURT: Objection sustained.
BY MR. RICH:
Q. You talked about showing us a diagram that shows how many submucosa glands there are. I guess we would like to see the next slide.
A. So when you go home tonight, you can say you see what

the nose looks like. This is a human turbinate. This is the part of your nose that, if you tried to reach your throat, would stop you. It's the part of your child's nose that he reaches with his little finger.

I think it's kind of interesting. This is the epithelium and the base of the membrane. And this rich thick layer here, this is the mucous producing glands. You can see how copious it is. And then this inner part is why the nose can get swollen fairly readily. These are venous sinusoids. And it's one of the only parts -- that and genital areas are the only parts of the body that have this venous sinusoidal system. So you can engorge this area by putting blood into your -- and it's one of the two mechanisms for getting congested. So the nose, to me, it's fascinating. I spent a lot of time studying it. There is a lot of inflammatory cells in this area, but this is what your nose looks like, microscopically.

Q. Can you show us where the glands are?

A. These are the glands. This very thick area right here. It's why you can make so much mucous so quickly.

Q. Now, I believe we have a video of a mucociliary area. Can you explain what is going on as we watch this?

A. First of all, these are the cilia and they're beating very rapidly. You can see they're moving things along. And these are some coli-particles (phonetic) put on the nose and

you are looking at the movement of mucous across the surface of the epithelium. You can see how quickly it moves.

Q. Is more information on these issues available in the articles incorporated into your expert report: How and Why the Nose Runs, Human Nasal Host Offense in Sinusitis, and Mediators of Allergic Rhinitis? They're in your binder as Exhibits 356, 357, and 358.

A. Yes. And then, of course, there is much more in the rest of the CV as well. Yes, they cover many of these areas.

Q. I would just like to turn very quickly to the topic of generally the administration of nasal sprays.

A. Right.

Q. And you have in front of you a brand new bottle of Nasacort AQ. And if you could just demonstrate how, when using a nasal spray like Nasacort AQ -- you don't actually have to use it -- you would use it.

MR. GRACEY: Your Honor, if I could object again. Same objection. Outside the scope of his expert report as far as this particular product.

MR. RICH: Your Honor, we're not suggesting that it's product specific. I'm just having him show how one uses a nasal spray.

THE COURT: The objection is overruled.

THE WITNESS: So I can do this?

MR. RICH: Yes.

THE WITNESS: So these nasal sprays, we do this all the time because we want to make sure the patient does it correctly. You know, shake it up. I think, I heard today that changes the viscosity, but we just shake it up so it's all mixed up. And you put this nozzle into the nose, past the vestibule, aim it up and out to the inner corner of the eye, which sprays it directly at the place you want it to go for distribution throughout the nose. And we usually instruct the patients to take a short sniff when they spray. And so it's simple procedure. If done properly, it works very effectively.

BY MR. RICH:

Q. **There are a couple things that came up in the opening that actually I don't think appeared in the expert reports. If I could just have you respond to them. One of the concerns that I seem to see that Barr has is that when you sprayed a nasal spray into your nose, there is a strong spray that creates a laminar flow. Do you have any experience with that?**

MR. GRACEY: Your Honor, again, I'll have to object again. This is nowhere in any of his expert reports.

THE COURT: Overruled.

THE WITNESS: Okay. So the spray comes out with some velocity. I don't know the velocity. And you are

sniffing. So it does have -- and it only has to go a very small distance before it hits the mucous membranes. And so it's probably laminar until it hits the mucous membrane, but it's a wide plume.

THE COURT: If it's "laminar," doctor, meaning?

THE WITNESS: Laminar is like an airplane, if you look at the flow of air over a wing, it's smooth, versus turbulent. So it would probably go back in a wide -- the plume, actually, you can see it. This is nothing different than any other spray. The plume is fairly wide, so it spreads out. It should cover much of the surface. But the way we aim it, it's aimed so it goes up to the top or middle part of the nose, preferentially.

BY MR. RICH:

Q. One of the other concerns we heard in Barr's opening that actually doesn't appear in the expert reports for any expert was that congestion in rhinitis patients might have an impact on the distribution of Nasacort AQ in the nose. Do you believe that such congestion would prevent Nasacort AQ from reaching the frontal sinus?

MR. GRACEY: Your Honor, if I could object.

THE COURT: Overruled.

MR. GRACEY: This is not the frontal sinus.

THE WITNESS: I think the congestion, if anything, would help getting deposition in the anterior part

of the nose at the entrance of the frontal sinus because you would have less airflow to the back of the nose which is not where the frontal sinus is. So if you are asking me would congestion stop it, I would say it's the opposite. It would most likely enhance the deposition of the product at the area of interest.

BY MR. RICH:

Q. And if the patient continues to take Nasacort AQ hopefully in compliance with the doctor's prescription, would that affect congestion in any way?

A. Yes, of course. That's why you use the product. This is the best product on the market to reduce congestion. So over the course of one or two days, congestion would largely disappear.

MR. RICH: Thank you, doctor.

Your Honor, I have no further questions.

THE COURT: Counsel, you may cross-examine.

CROSS-EXAMINATION

BY MR. GRACEY:

Q. Good afternoon, Dr. Kaliner.

A. Nice to see you again.

Q. Nice to see you as well. Taras Gracey. As you may recall, I took your deposition earlier this year. I just want to establish a few things about your expertise and start out with a little bit about what you have done.

First, you are not a chemist. Correct?

A. **I'm not a chemist.**

Q. **Or a molecular biologist?**

A. **I know something about molecular biology.**

Q. **Do you have a Ph.D. in molecular biology?**

A. **No. But as part of the research, it's all molecular biology.**

Q. **And you are not a pharmaceutical scientist. Right?**

A. **I'm not a pharmaceutical scientist.**

Q. **And you are not a radiochemist?**

A. **No, I'm not a radiochemist.**

Q. **Or a radiologist?**

A. **Nor a radiologist.**

Q. **You, in fact, never designed a pharmaceutical formulation?**

A. **Well, I did discover Nasal Atrovent and gave it to Rorer Ingelheim, so I guess that counts to an extent.**

Q. **Did you ever design a nasal spray?**

A. **Nasal Atrovent is a nasal spray. We didn't design the spray. We designed the chemistry of the product, itself.**

Q. **Okay. You have never used a PET scan in all of your years of treating patients?**

A. **I have never seen a PET scan used.**

Q. **And you don't do surgery either, do you?**

A. **I don't do surgery. I see many surgical patients.**

Q. **You've never designed a co-solvent system, have you?**
A. **I don't know exactly what that is.**
Q. **Okay. And along the same lines, you don't know what Avosil 591 is?**
A. **I do now. The answer is yes, I do know.**
Q. **And that is part of this case?**
A. **I didn't know until a few months ago.**
Q. **Same with regard to Avosil 611. Prior to this case, you didn't know what Avosil 611 was?**
A. **That's true.**
Q. **Now, Dr. Kaliner, you are obviously here as an expert witness for Aventis. Correct?**
A. **That's correct.**
Q. **And you are being paid for your time today at about $500 an hour. Right?**
A. **While I'm here in Wilmington I am.**
Q. **But this isn't really the first time you have consulted with Aventis, is it?**
A. **No, I have a very long relationship with Aventis and many other companies.**
Q. **In fact, we saw a chart that Dr. Georges talked about in his testimony that showed the various predecessors. And it's true that you have done various consulting for those various predecessors over the last 25 years. Right?**
A. **That's correct.**

Q. **Now, Dr. Kaliner, nowhere in your expert report do you state that Nasacort AQ enters the frontal sinus, do you?**

A. **You asked about what is in my expert report. I'm certain I said that it's sprayed on to the area of the frontal sinus but you just asked the question -- can you repeat?**

Q. **Sure. Nowhere in your opening expert report do you state that Nasacort AQ enters the frontal sinus, do you?**

A. **And I'm sure I said that it enters the area of the ostium frontal sinus.**

Q. **Let me just say it one more time. And you have your report there. It's parts of your binder. You're free to look at it. It's only seven or eight pages, I believe. Nowhere in that report do you state that Nasacort AQ enters the frontal sinus?**

A. **That's right. And I have no way of knowing that answer, but the answer is I didn't say that.**

Q. **Right. Okay. Thank you. In fact, nowhere in your expert report do you state that Barr's proposed ANDA product at this point enters or would enter the frontal sinus, do you.**

A. **I'm sure I didn't say that.**

Q. **All right.**

MR. RICH: Your Honor, if I may?

THE COURT: Yes.

MR. RICH: On redirect, I believe the door has been opened to ask the questions that I had wished to ask with regard to entrance to the frontal sinus.

THE COURT: Okay.

MR. RICH: Thank you, Your Honor.

MR. GRACEY: Your Honor -- well, that's fine.

BY MR. GRACEY:

Q. **Dr. Kaliner, nowhere in your expert report do you state that Barr's ANDA product infringes the patent claims at issue, do you?**

A. **I don't think I said anything about Barr's ANDA product in any context.**

Q. **And just so the record is clear, you are not a patent lawyer, are you?**

A. **I'm not a patent lawyer.**

Q. **Now, you have tried to treat patients with frontal sinusitis with a nasal solution, haven't you?**

A. **I've used off-label nasal solutions in the treatment of sinusitis frequently.**

Q. **Yes. And a nasal solution is something different than an aqueous nasal spray such as Nasacort AQ that is at issue in this case. Is that right?**

A. **That's correct.**

Q. **All right. Now, in using that nasal solution, you have the patient literally upside down; isn't that right?**

A. **That's correct.**

Q. **Okay. And you put the patient upside down to reverse gravity, to use your words. Isn't that right?**

A. **Yes, that's correct.**

Q. **In fact, I think what we heard you say a little bit earlier, but you certainly stated at your deposition, that it's your belief that the frontal sinus is relatively infrequently -- infrequently affected because the drainage is assisted by gravity. Isn't that right?**

A. **Yes, I think that is part of the reason it doesn't get infected.**

Q. **Okay. And you put the patient upside down in an effort to reach the frontal sinus. Right?**

A. **I think you are misconstruing. We were talking about primarily treating ethmoid and maxillary sinus disease because frontal sinus is relatively infrequent, and I don't aim that therapy at the frontal sinus, I aim it at the ethmoid and maxillary sinuses. It's slightly off. They're not quite the same way of treating.**

MR. GRACEY: Okay. Let's take a look at your deposition. Can we have Page 109, Line 18.

Permission to approach, Your Honor?

THE COURT: Yes.

(Documents passed forward.)

MR. GRACEY: He is going to play you the clip.

THE COURT: What page that is, counsel?

MR. GRACEY: This is Page 109, Your Honor. And we're going to see the video clip here.

(Audio not working, just deposition page placed on screen.)

MR. GRACEY: I'll read it.

BY MR. GRACEY:

"Question: All right. Why is it that you need to put the patient horizontal to the ground as opposed to being supine?

"Answer: The frontal sinus is relatively infrequently affected because the drainage is assisted by gravity.

"Question: So you want to reverse?

"Answer: So you're reversing gravity."

Do you recall saying that, Dr. Kaliner?

A. **Yes.**

Q. **Now, let's talk a little bit about putting the patient upside down and why you did it. Do you recall that at your deposition I asked you if you had tried to treat a patient suffering from frontal sinusitis? Do you recall that?**

A. **Well, if you say so. But I mean the answer is that in real life, I use this to treat maxillary and ethmoid diseases.**

Q. **Let's take a look at your deposition again, at Page**

102 this time. All right. The question I asked was:

"Question: Have you had patients who, when you have taken the proper history, done the proper test, whether it's the light and/or tap test, you determine that there's possible or likely inflammation in the frontal sinus? Have you had any patients like that?"

A. **Oh, sure.**

Q. **Your answer was:**

"Answer: Yes.

"Question: All right. Have you done any therapeutical trials with those patients?

"Answer: A clinical trial. You mean trials of experimental approaches?

"Question: Yes.

"Answer: And the answer is yes, with some. We have treated patients with solutions of corticosteroids and using postural positioning of the head in such a way that we try to get materials into the frontal sinus with some success."

And then my next question was:

"Question: Explain what you mean by putting them in a postural positioning.

"Answer: Having the patients fill the top of their nose while their head is in an upside position so they're 90 degrees to the floor.

"Question: All right. Head to the floor, feet to the ceiling?

"Answer: Well, feet doesn't have to be to the ceiling. But the head is to the floor."

All right. So again, Dr. Kaliner, I ask you, you have attempted to treat patients suffering from frontal sinusitis by turning them upside down on their head and floating the nose with the nasal solution. Isn't that right?

A. **That's correct.**

Q. **Now, it's a little more than that, isn't it? In fact, once you have the patient upside down, you actually take a catheter --**

THE COURT: You can take that down.

MR. GRACEY: Take it down.

BY MR. GRACEY:

Q. **You actually add a catheter to the process. Isn't that right?**

A. **Well, that is how you introduce the solution into the nose.**

Q. **All right. And you do that in an attempt to flood the nose with the nasal solution. Right?**

A. **The patients are upside down so it's the only way they can administer something to the nose is through a syringe-and-catheter arrangement.**

Q. **And you are attempting to flood the nose. Isn't that right?**

A. **Well, no. We already are putting in 10 milliliters. The nose holds considerable more than that so we're not flooding it. We certainly are putting in solution to try to get it in primarily to the ethmoid and maxillary sinuses.**

Q. **All right. Let me turn your attention to Page 106 of your deposition. Again, I'll read this to you. If we can have 106, Line 13 please.**

"Question: Okay. And I think you anticipated in answer to my next question but just so I'm clear. What is the theoretical basis -- yeah. What is the theoretical basis that makes it more likely to get into the frontal sinus than a nasal spray?

"Answer: A nasal spray is a small volume. So you're putting 100 microliters or 50 microliters.

THE COURT: Counsel, hold on. You are going kind of fast. You have court reporters here.

MR. GRACEY: You're right.

THE COURT: Please, let your IT guy get it up on the screen.

MR. GRACEY: I'm sorry, Your Honor.

BY MR. GRACEY:

Q. **All right. I'll read the answer a little slower.**

"Answer: A nasal spray is a small volume so you

are putting 100 microliters or 50 microliters, depending on the spray. And where I'm using 4 ounces to 120 milliliters of material, and I actually fill the top of the nose, and I'm pretty sure that the ostia is going to be underwater, level of liquid."

Do you see that?

So you are attempting to fill --

THE COURT: You have to say yes or no.

THE WITNESS: Yes, yes. I see that.

BY MR. GRACEY:

Q. **So you are attempting to fill the nose. Isn't that right?**

A. **The top of the nose, that's correct.**

Q. **But even then, even using that posturing, if you will, the putting the patient upside down on their head, using a nasal solution, not spray like we have here, and flooding the nose, even then, you don't know for a fact that that corticosteroid reached the frontal sinus, do you?**

A. **I've never, I've never done a visualization system but I can tell you clinically it usually works and the patients get better.**

Q. **All right. I'll just ask you one more time. You don't know for a fact that the nasal solution, again not spray, is actually reaching the frontal sinus even taking all the steps that you described?**

A. That's correct. I never visualized it.
Q. And you don't know that for a fact. Isn't that right?
A. That's correct.
Q. Okay. Thank you. Now, this procedure that you described for me at your deposition, this is not something that an ordinary clinician would even be aware of, is it?
A. No. We, as I said before, we take care of very difficult patients, and we are not only doing typical treatment plans.
Q. And it's not something that an ordinary clinician would even have done. Isn't that right?
A. That's correct.
Q. All right. Now, we talked about your attempts of getting to frontal sinus with the nasal solution but you haven't tried, have not tried to treat a patient suffering from frontal sinusitis, which, I think we can agree on, is inflammation of the frontal sinus. Right?
A. Yes.
Q. With an aqueous nasal spray such as Nasacort AQ; isn't that right?
A. No, it's wrong. We used aqueous nasal sprays as the initial treatment in all patients that have sinusitis, every one of them.
Q. I think you misunderstood my question. You haven't taken a patient, made them stand on their head and put a

nasal spray in their nose in an attempt to treat the frontal sinus?

A. No, and I probably won't.

Q. And that is because -- right? That is because the nasal spray is a small volume of material compared to the amount used in the nasal solution. Isn't that right?

A. Well, that is one of the many reasons why I wouldn't do what you are suggesting.

MR. RICH: In fact, if we can, Jeremy, put that Page 106 we just had up there, Lines 13 to 22. Actually, if we go up to Line 7.

Now, this is in the context of asking if you haven't done it with a nasal spray.

BY MR. GRACEY:

"Question: You haven't done it. Okay. Why haven't you done it?

"Answer: Because we've been using this liquid formulation that theoretically -- to me, it is a more theoretical basis of actually getting into the sinuses because there's more volume."

And you continue on in the next answer, when you say:

"Answer: A nasal spray is a small volume.

So I come back to my question, Dr. Kaliner. The reason you don't put patients on their head and have them

put a spray in is because of the small volume and you don't believe that will hit the frontal sinus, do you?

A. Let me explain. You are talking about patients that come to me with difficult to manage sinus diseases, have been through surgery. We're dealing here primarily with allergic rhinitis. Only a small percentage of those patients have problems with their sinuses so it's a whole different context.

You're really changing everything we talked about in a way that I don't think is quite kosher. I am treating sinus disease, trying to get -- and then patients who have failed nasal sprays, not just Nasacort but the whole range of nasal sprays, because they don't work adequately in those patients. And I try things that are quite adventuresome and aggressive and oftentimes effective.

Q. But isn't that the point? Isn't that the exact point is that the nasal sprays don't work and then they come to you? The tough patients come to you and that's when you invert them on their head?

A. These are patients who have already had surgery and multiple antibiotics and they are have disease sinuses. And, yes, in those patients, we do use nasal sprays as part of the treatment, but they have not been adequate so we have to find another way to get the steroids into the sinuses. And, again, overwhelmingly it is ethmoid and maxillary and

not frontal.
Q. However, as we have looked at your deposition here today, when you do have a patient with a frontal sinus problem and they come to you, it's clear that they are coming to you because the spray isn't working, that's when you invert them. Isn't that right?
A. That would be right.
Q. Now, Dr. Kaliner, have you ever looked at the prescribing information for Nasacort AQ?
A. The package insert?
Q. The package insert.
A. Yes, I have.
Q. Does it say anywhere that a patient should stand on their head when administering Nasacort AQ?
A. No, it doesn't say. Outside of my office and maybe 100 specialists in the United States that I know of, in Europe as well, nobody does this.
Q. Okay. All right. Now, you have stated that you believe -- you say that here today and say at your deposition, I believe, that you believe that the frontal sinus is actually more accessible than the maxillary sinus. Do you recall saying that here today?
A. Yes. The entrance to the frontal sinus is more readily accessible to sprays than would be the maxillary ostium.

Q. **Now, Dr. Kaliner, do you know Dr. Berridge?**
A. **Yes.**
Q. **And you know he is going to be testifying here today on behalf of Aventis?**
A. **(Nodding yes.)**
Q. **Is that a yes?**
A. **Yes.**
Q. **And you are familiar that he had done, I think Aventis's counsel and Barr's counsel had mentioned some PET studies he had done regarding Nasacort AQ and where it deposits. Right?**
A. **That's correct.**
Q. **All right. Now, as of your deposition, you hadn't reviewed Dr. Berridge's data, had you?**
A. **No, I hadn't.**
Q. **And I think you stated to me that you believe that if that data showed that there was more deposition of Nasacort AQ on the maxillary sinus than on the frontal sinus, then it is easier to reach the maxillary sinus than the frontal sinus. Do you recall telling that?**
A. **I have to admit I don't.**
Q. **If you look at Page 419 of your deposition.**
MR. GRACEY: Let's start with, let's put up, start at Line 14 and we'll go down from there. This is 415. Maybe 419. Right there. Okay.

BY MR. GRACEY:

Q. **And I ask:**

"Question: Did you review the Berridge deposition data on the maxillary and frontal sinuses?

After objections, you said:

"Answer: It's an easy answer. No.

And I asked you:

"Question: Okay. If that data showed there was more deposition on the maxillary sinus than on the frontal sinus, which sinus would be, in your opinion, easier to reach?

Again, there are more objections. And you stated:

"Answer: I always tell everybody data is data. If the data says that -- whatever the data says is what it is. If they showed more deposition on the maxillary, then it's easier to get in that model to the maxillary.

"Question: Then the frontal side?"

I don't know if that was a transcription error, my misstatement but it was a "frontal sinus" and you answered:

"Answer: Then the frontal."

All right. Now, do you recall testifying to that?

A. **As you will see, this is the last comment of a**

four-hour deposition. And now that you pointed it out, I assume I said that.

Q. Okay.

A. The answer is no, I don't remember it.

Q. Do you deny you said it? Let's put it that way.

A. I'm sure I said it.

Q. Okay. Thank you. Now, I would like to show you --

MR. GRACEY: If I may approach, Your Honor?

THE COURT: You may.

(Documents passed forward.)

BY MR. GRACEY:

Q. All right. If you will look up with me at DX-5, this is Dr. Berridge's, one of his reports. Do you see that, the cover of the page?

A. Yes.

MR. GRACEY: All right. Now, if you'll look at Page 12? And if we can focus on the bottom. And if we can highlight maxillary and frontal for Nasacort.

BY MR. GRACEY:

Q. All right. Bearing in mind, Dr. Kaliner, what you just stated, it's the data is the data. You would agree with me here that it identifies for Nasacort AQ 1.67 under maxillary and zero under frontal sinus. Do you see that?

A. I do see that.

Q. At the risk of asking a sophomore question, 1.67 is

greater than zero. Isn't that right?
A. I think so.
MR. GRACEY: Thank you, Dr. Kaliner.
THE COURT: Any redirect?
MR. RICH: Hopefully just a few, Your Honor.
THE COURT: All right.
REDIRECT EXAMINATION
BY MR. RICH:
Q. If I could start with where we just left off and ask have you ever reviewed this final report before?
A. No, I have never seen it before.
Q. Is this within your specialty?
A. No, I don't know anything about this report. I could comment on 1.67 and zero, though. That's it.
Q. Fair enough. I'm glad the answer came out right on that one.
THE COURT: When you say "this report," do you want to identify the report?
MR. RICH: Yes. Thank you very much, Your Honor. It's Defendant's Exhibit 5, The PET study of the Distribution and Kinetics of Nasacort AQ and Flonase.
BY MR. RICH:
Q. And Barr's counsel actually solicited this already, but you're not an expert in PET studies, are you?
A. I have never done a PET study in my life.

Q. **I want to turn to another of the subjects that Barr's counsel inquired into and he spent quite a bit of time on, which is sinusitis. Now, is Nasacort AQ indicated, approved by the FDA for sinusitis?**

A. **No, Nasacort AQ is only approved for seasonal and perennial allergic rhinitis.**

Q. **Are they the same condition?**

A. **Not at all.**

Q. **Can you tell me some of the differences between the two?**

A. **Well, allergic rhinitis is inflammation of the nose and the sinusitis is inflammation of the sinuses. They're contiguous but they're very different diseases with a whole different spectrum of symptoms and the treatment is entirely different between one and the other. They're not at all the same.**

Q. **One of the other things he asked you about with regard to sinusitis and this whole postural issue and flooding the nose with the solution. He asked you if you knew for a fact that the steroid definitely got there. In your mind, is it more likely than not that in your treatments for sinusitis that the steroids get to the frontal sinus?**

A. **I know they have to get to the entrance to the frontal sinus but I can't go past that. They certainly get to the entrance, and I believe the frontal sinus is ventilated with**

every breath and so air is going into the frontal sinus and you're sniffing it and directing it at the frontal sinus and so I would be surprised if some of it doesn't get into the frontal sinus.

MR. RICH: If we could bring up the slide with the nose with the turbinates?

Back a couple. Actually, I guess that is the turbinates. So it should have been there. I apologize. This picture.

BY MR. RICH:

Q. Now, I asked you before about the pathway to the frontal sinus. Do you have an opinion as to whether there is air exchange with the frontal sinus?

A. The frontal sinus is, in you and me and you, sir, is om open communication to the air right now. And so as you are breathing, there is open communication. It may be a small tract but it's open and you can breathe. There is ventilation that goes on right now, every single breath we're taking.

Q. Do you have any real life example that would demonstrate that?

A. Well, most of us have flown. We might have trouble popping our ears because the eustachian tube is a closed space, but none of us have ever had to pop our sinuses. They're in open communication. When it changes pressure, it

equilibrates just as an open space would equilibrate. There isn't a single person in this room who doesn't have sinusitis as the only circumstance that ever had problems with their frontal sinus when they fly.

Q. One last set of questions. I won't promise one last question because that would be dishonest. You were asked about consulting for Sanofi-Aventis or RPR. Correct?

A. Correct.

Q. Have you consulted for anyone else in the allergy asthma field?

A. I believe I have consulted with every single company that makes any product dealing with allergies and asthma over my 35-year career; and so, you know, I'm familiar with every single company from the inside.

MR. RICH: That's all I have, Your Honor.

THE COURT: All right. Thank you, doctor. You may step down. Let's take a short stretch break.

(Recess taken.)

THE COURT: Please be seated. Your next witness.

MR. RICH: Your Honor, Allison Baldwin will be presenting the next witness.

THE COURT: All right, counsel.

MS. BALDWIN: Good afternoon. Plaintiffs call Dr. Mark Berridge.

... MARK BERRIDGE, having been duly sworn as a witness, was examined and testified as follows ...

MS. BALDWIN: Your Honor, may I approach?

DIRECT EXAMINATION

THE COURT: You may.

BY MS. BALDWIN:

Q. Good afternoon, Dr. Berridge.

A. Good afternoon.

Q. Could you provide us with just a brief description of your educational background?

A. Certainly. I got a Bachelor's degree in chemistry from Carnegie Mellon University. After that, I went to Washington University in St. Louis for graduate school. It turned out that was one of the three places in the United States that were doing PET scanning at the time. I got my Ph.D doing radiopharmaceutical chemistry and positron tomography.

After that I went for a postdoctoral stint for two years at the Atomic Energy Commission Marseilles, which was one of the world's leading facilities in PET research at the time.

Q. What is your current position, Dr. Berridge?

A. I am president of a small company, 3D Imaging in Little Rock, Arkansas, that does imaging research, specifically PET, for drug development research. And I am

also a professor at the University of Arkansas Medical Sciences. I am professor of radiology in the medical school. And I am also professor of pharmaceutical sciences in the School of Pharmacy.

Q. Where were you employed prior to joining the University of Arkansas?

A. Then I was in Cleveland where I was also president of a similar small company for drug development research, using positron tomography. And I was also professor of radiology and chemistry at Case Western Reserve University.

Q. Dr. Berridge, as you have already heard from the openings and the witnesses before you, PET is of primary interest in this case. Could you explain to us your background with PET? How long have you worked in the field?

A. Well, I started working with PET when I was a graduate student. So that is over 30 years ago.

Q. Are you involved in any research organizations or professional organizations in the field of PET?

A. Yes. I suppose primarily would be the Society of Nuclear Medicine. I have been a member for almost all of that 30 years. I have been heavily involved in the society. I have been involved in the leadership of the society, and served on several committees, including a PET committee and a Pharmacopeia committee.

I have also been involved in the Society for

Non-Invasive Imaging and Drug Development, which is now part of the Academy of Molecular Imaging. I am involved in the leadership of both groups. I am a member of the Board of directors of SNIDD, as we call it, and the secretary of that organization as well.

Q. **Dr. Berridge, I caution you to not turn away from the microphone because your voice is very soft. It helps us all to be able to hear you.**

A. **I am sorry. I will try to remember to keep this up.**

Q. **What amount of your time is spent in using PET in research?**

A. **Essentially all of it. I have a small amount of administrative functions. But I spend most of my time in PET research.**

Q. **What type of research do you conduct using PET imaging?**

A. **The object of our company is drug development research, and that is where I spend most of my time. I also have an academic mission supporting other research investigators at the University of Arkansas Medical Center.**

Q. **How long have you been using PET imaging in design and development?**

A. **The first PET study that I ran began was in 1990. I was actually doing radiochemistry for drug development even before that.**

Q. **Were you the first in your field to use PET in nasal and pulmonary inhaled drug studies?**

A. **I believe this type of study, we were definitely the first to do that. And as far as I know, we are still the only laboratory that is doing this sort of research.**

MS. BALDWIN: Your Honor, plaintiffs tender Mark Berridge as an expert in the field of Positron Emission Tomography.

THE COURT: Any objection?

MS. RURKA: No objection.

THE COURT: He is accepted as an expert.

BY MS. BALDWIN:

Q. **Dr. Berridge, do you know why you have been asked to testify here today?**

A. **Yes. I believe I am a fact witness for the experiments I performed in 1996 and '98, 2002, and also an expert witness for this type of positron tomography.**

Q. **As part of your role as an expert witness in this case, did you prepare any reports outlining your testimony for today?**

A. **Yes. I prepared two reports.**

Q. **Before we start discussing the PET studies that you conducted on Nasacort AQ, could you first provide the Court with a brief background explanation on what PET is?**

A. **PET is fairly complex. We actually have a video that**

was prepared by Rhone-Poulenc Rorer after the first study, and an excerpt of that does a pretty good job of explaining the technique.

Q. Could you pull up P demo 140 for us, please.

A. This video begins showing the drug molecule, which actually triamcinolone acetonide. We can focus on that carbon in the upper right corner. You can go ahead and roll the video.

That carbon is where the carbon 11 radiolabel is placed. It does not change the drug molecule at all. So we are looking at the active ingredient of the drug.

Q. The active ingredient of --

A. Stop that again.

Q. The active ingredient you are looking at here is the active ingredient of Nasacort AQ. Correct?

A. Triamcinolone acetonide is the active ingredient of Nasacort AQ, yes, it is. The nucleus of carbon 11 is unstable, it is radioactive.

Go ahead and run it.

It decays by emitting a positron. A positron goes a short distance across space and encounters an electron. It is something right out of Star Trek, the two annihilate and they produce two gamma rays that come out in opposite directions, which is a fine point of physics, perhaps, but it is the feature that makes PET work as well

as it does and gives us quantification.

If we go ahead and roll.

The detector in the PET camera is a ring around a patient. They impinge on both sides, and the camera detects that the event occurred along the line between those two detectors.

A few million counts later you end up with an image of the radioactivity distribution that was present in the body that was placed in the camera, in this case, a cloud that represents the distribution of Nasacort AQ in the sinus cavity -- in the nasal cavity.

Q. What we are looking at right here, and is that an actual PET image?

A. That is an image taken from one of the PET studies, I believe a 2002 study.

Q. So every point in that image corresponds to what?

A. Well, each point in the image represents -- it's a number, actually, in the computer. It represents the amount of drug that was present at that point in space at that time.

Q. So is this image just one time?

A. This is one time point. The intensity of every point in that image represents the quantity of drugs. So where it looks brighter, there is more drug deposited, and where it looks dimmer, there is less drug.

Q. **How does PET measure how the drug distribution changes over time then?**

A. **Similar to still photography and movie photography, you have a frame, as we call it, which is a single image like this. Now, that can be acquired in as short as a few seconds or as long as many minutes. That frame gives you one picture. If you put those frames back-to-back, as we do, you get a series of still pictures, which can be put together to give you a time-lapse view of it and can actually be put together to form a movie of the distribution over time.**

Q. **Let's talk about the first PET study you did on Nasacort AQ. When was that study conducted?**

A. **We ended that in 1996.**

Q. **If you look in that binder placed in front of you at PTX-528, do you recognize that document?**

A. **Yes, I do. That is the final report from that study submitted to Rhone-Poulenc Rorer.**

Q. **That is the report of the data from your 1996 PET study of Nasacort AQ?**

A. **That is correct, yes, it is.**

Q. **Dr. Berridge, could you walk us through how you actually conducted the 1996 PET study of Nasacort AQ?**

A. **Absolutely. Actually, there is another video that Rhone-Poulenc made at the time that helps very much in that.**

Q. **So this is actually you conducting the 1996 PET study?**
A. **Yes. These are not actors. That's me right there. The technician that you see is the technician who performs the studies. The study nurse, you will see, is the study nurse who was involved in all of these studies.**
That shows the PET counter that we used, and the apparatus that was used for holding the volunteer.
Q. **It's a little hard for us to see on this big screen. If you could point out for the Court, it's hard to actually see, the volunteer might be easier for you to see on your screen.**
A. **The volunteer just shows up much better on the small screen. The head of the volunteer is down here. You can see this head holder. It's black. And then it's being held by these large Plexiglass, essentially, poles, and a rigid apparatus which is bolted to the scan bed.**
Q. **Is this normally the way a PET study is conducted?**
A. **No. This is something we invented for this study alone.**
Q. **Why?**
A. **Well, we didn't know, as we began this study, whether you were going to observe that the drug is very fluid, or whether it would stay exactly where it was sprayed, as they would like to claim.**
We wanted to know accurately whether that was

the case.

If you were to perform this study with someone laying on their back, the gravity factor is pushing backwards. Normally, when you take in the gravity factors, it's facing downwards. And we did not want to have an artificial enhancement of the study results by the fact that the person was on their back and might increase the apparent deposition of the drug back into those turbinate regions.

So we wanted to scan them with their head face-up.

So we had to develop this apparatus to hold them, support their weight, and keep them immobile in space during the scanning, because it's like time-lapse photography.

If you roll that, the volunteer is being put into place. The head goes back against that rigid head holder. There is a thermoplastic face mask which is being applied to the volunteer. When it is worn, it is very flexible. It is the same material that is used to make casts for broken bones sometimes.

That face mask then hardens on the volunteer. We left out some time there while it did so. That is part of the support and positioning structure of the apparatus, as well as that chin strap that can be seen. The volunteer is also supported on the chest against the side of a PET

counter, and they are sitting on a bicycle seat, which can't be seen.

Now what you are looking at there is the drug administration by the study nurse, because the volunteer has no use of their hands, and they practiced and coordinated that administration according to package insert instructions.

Q. What is that red line in the picture?

A. Yes, there are actually three positioning lasers, one from each side of the camera and another one that was mounted to the wall during those studies. Those just provide a little bit of laser light that doesn't move. We use that to mark the volunteer's face and the mask, and to ensure throughout the study that there isn't any motion or if any small motion occurs, to correct for that motion and put them back where they belong.

Q. Dr. Berridge, how long was someone stuck in this position?

A. Well, it looks much more difficult than it is. I have hung in that thing myself. But I can't call it comfortable. If there are any Catholics in the room, they might have experienced that.

But it is a kneeling position. You can tolerate it actually for quite a long time. We had one volunteer go about two hours. But most of them could tolerate only 40

minutes to an hour.

Q. What happened after that?

A. Well, they were given the opportunity to tell us when they no longer wanted to stay in that position. This is part of normal protocol for any kind of research study. So they were able to tell us that they wanted to get up. When they did, at the end of that frame, we would move them, take that apparatus off the bed and place them back on the bed in the supine position, facing upward, and put them back in the scanner and continue with the scan from that point.

That all took about no more than about 45 seconds to accomplish. And we corrected the data acquisition, the data analysis for that loss of time.

Q. So after you completed this PET scan, is there any other data that you need in order to analyze the data actually collected during the scan?

A. Yes, absolutely, because as you might have noticed when you looked at that image, you don't see a lot of anatomy in that PET scan. What we needed to do was align that with an anatomic image. So we took a magnetic resonance image, an MRI scan, to get the anatomy.

Q. How does the MRI scan help you get the anatomy for that PET scan?

A. We overlay that with the PET scan and then use the MRI anatomy to help us define the regions that are of interest

in the PET scan.

We have an image to show for that.

Q. Could you pull that up, it's PTX-510.

Am I correct, this is actually in your 1996 study report?

A. This was part of the report, yes. On the top there, you can see, this is the MRI scan. It's a three-dimensional data set, just like the PET scan. But these are three different slices in different planes through the image. This is the PET scan in this row, in those same three slices. This is a different scan, a different scan, a different subject, than the previous one.

On the bottom you can see the result after they have been superimposed, showing the overlay of the PET scan with the anatomy.

The process of superimposition involves more than what we can just see here.

Q. Who actually does the superimposing of the images?

A. There was a trained data analyst who spent his life doing this sort of thing and did all of that, actually created some of the software to do it.

Q. Am I right, Dr. Berridge, that the alignment technique that was developed here has actually been awarded honors by your peers?

A. After that software was created, yes, it was used and

applied to a clinical situation with prostate cancer. And the use of that technique and superimposition with anatomy won us the 2000 Society of Nuclear Medicine Image of the Year designation.

Q. Is this standard in the software now?

A. It has now become a part of the package of software on every commercial PET scanner.

Q. Once you have completed the scan and overlaid the images, how do you determine the actual amount of radioactive Nasacort AQ deposited in the nasal cavity of the volunteer?

A. Well, that was done by creating regions of interest on the PET scan, so that we could localize the individual areas that were interesting to us, and divide that image up into the amount of drug that was deposited in the various regions. We can show you how that worked as well.

Q. What are we looking at here, Dr. Berridge?

A. It looks a little messy. It is a screen shot taken from one of the computers being used at the time. We have drawn, just for ease of showing it, a little bit of the outlines of the anatomy on these scans, to show where the skull is and where the eyeballs are. This is the MRI scan from one of the volunteers.

Q. So the PET, you don't see the PET scan on this?

A. There is no PET data on this at all.

Q. **How do you determine what the regions of interest were?**

A. **Well, we are looking for anatomic localization. So at this point we don't need the PET scan. We define the images on the MRI.**

In fact, they are just cubicle regions that we used for this study. We were somewhat limited in our computer capacity at the time.

So this is the array of cubes that was used to be studied.

Q. **I guess I am a little unclear. These boxes are the cubes, are these the regions of interest?**

A. **These are the initial regions that we used. Many of these small cubes -- the cubes, of course, are stacked, like a child's blocks would be. And these are the slices, the two-dimensional slices through the three-dimensional array, always remembering this is a three-dimensional data set.**

When you cut through a cube, you get a square. And this is how they were initially aligned. That grid of squares, or cubes, was positioned. Now, bear in mind, of course, the data analyst didn't have to look at just three of these slices. The data analyst could scroll through the whole three-dimensional set and look at any plane through here. And they positioned the cube so that they would be best useful for the study.

Q. **Now, how do you assign a cube to an anatomical region?**

A. **Well, that was the task at the time. And what we did was we went through all of the cubes one by one. The data analyst for this portion of the procedure had a certified nuclear medicine physician who came down to assist, who was part of the study just for that purpose. And that nuclear medicine physician and the analyst went through cube by cube throughout the entire data set and decided which region each one of those cubes should be assigned to.**

Q. **How did you handle a cube that overlapped more than one region?**

A. **Well, that happened to some extent, of course. In fact, if you look down there, you will see these regions out the front, they overlap into the front of the nose, but they also contain some region of dead space. Then back in here, through the turbinates, we weren't really able to separate out those anatomic structures that we saw previously, where you can have the three different turbinates. We simply divided it into superior and inferior. Remember that through the study, we weren't really worried about specific anatomy as much as we were worried about what the distribution and extent of the drug was going to be.**

As long as we were consistent, it gave us good data we could analyze.

So we assigned those regions. Bear in mind,

also, that in that cloud, the intensity doesn't change very much as you go across space. So a little bit of overlap through that region didn't have a large effect on the result, and again, as long as we were consistent. But the other areas that it became more important was in the sinuses. The sinus back there, you have the frontal sinus, then out to the sides, which don't really show on any of these images, you have the maxillary sinus.

In that case, as we began the study, we didn't really expect to see uptake in the sinuses. We didn't know, but we had no reason to expect it necessarily.

In any case, we expected it would be small.

So we had to be very careful about that. We couldn't put a region and assign it to a sinus if that region had a chance of including data from a region that was going to clearly have drug deposition in it.

So we could only assign a region, and we have been talking about frontal sinus up here, we could only assign exactly that one cube, because we had to avoid any cubes that might overlap with other regions.

Q. Using this method, were you able to account for all of the administered dose of the radioactive Nasacort AQ?

A. That was another question, as we began the study, a serious question as to whether we would see everything and account for it. And, yes, we did. We showed that we were

seeing all of it.

Q. Now, once you gathered all this data from all the cubes, all the time points, all the volunteers, how do you analyze and draw conclusions from it?

A. It is a lot of data. If you approach that data set raw, you really have a very hard time wrapping your head around it.

What you need to do is display it in different ways for different purposes. So you can display it graphically -- first off, maybe tabular. You can just separate out the regions and show how much deposited in each region. You can do that for selected time points.

You can take all of the time points and put them together for each region and you can show a graph of the distribution over time.

You can look at the images, which gives you a completely different way of understanding the data, and has different information than the tabular data does.

Lastly, you could put it together in a time-lapse movie and show the distribution over time that way.

Q. Dr. Berridge, you talked about graphing it. Is there a certain shape of the graph that you expect from this type of data?

A. From almost all types of PET studies, there is a basic

curve shape that you tend to see.

Q. Did you prepare a graph to show us that general curve shape?

A. We do have some examples here of standardized curves to show you pretty much what to expect and what to look for in the data when you see the data.

The blue curve that you see there is a more simple case. In all cases you have an uptake phase, where the drug is being administered. And that's usually quite rapid. In this case it is a single inhalation. That deposits the material very quickly into the region, and usually stabilizes, and you get to a peak.

After that peak, you have a washout. That washout can be very simple. If there is only one mechanism that causes it to leave the region, it can be a mono-exponential curve, such as this blue curve shown here, which is what you might expect in this context if you had mucociliary clearance acting and only that.

If you have other things acting, you have more complex curves, where you have different rates of washout happening at the same time. So you have perhaps a faster rate for part of the material that shows you the initial, that you see initially. When that portion of the material has washed out, then you see the components of it that has a slower washout rate.

There could be two, there could be three, there could be four compartments in the data. And you can see them as different exponentials that come out of the data.

Q. Let's talk more specifically about the data that you actually obtained during the 1996 study. Did that data show this typical curve shape that you were expecting?

A. It did. All of it fit this same general family of curves.

Q. Could we look at the anterior regions of the nose, which in 1996 I think you referred to as the frontal cavity?

A. Yes, that's what we called it then. This graph shows Nasacort AQ from that 1996 study.

Q. Why are there three lines?

A. That is the data from the three different volunteers, each one shown individually. There is some variation in the amount of uptake that was left in that cavity, as you can see. And then they each show this initial phase. It is not quite as severe as what was shown in the stylized curve. And then they show a more prolonged retention or slower washout phase after that.

Q. So does this graph of the data from the frontal cavity in the 1996 volunteers show deposition on Nasacort AQ in the frontal cavity?

A. You can see clearly that there is Nasacort AQ in the frontal cavity, yes.

Q. **Does it shows that Nasacort AQ is retained for about an hour in the frontal cavity of these volunteers?**

A. **Yes, those curves stay well above the bench line, all the way out past an hour.**

Q. **How about the turbinate regions?**

A. **That would be the other end of the cavity and we can show that. These came a little closer together. This again is the same study, the same three volunteers. This is just the entire turbinate regions combined. Again, we have the same curve shape. We have a peak at a fairly large amount of the administered dose, applying the turbinate. We see that biphasic washout again. And we see retention well out past an hour.**

Q. **So does this graph show that Nasacort AQ is deposited in the turbinate regions for the volunteers in 1996?**

A. **It certainly does, yes.**

Q. **Is it there for about an hour?**

A. **Absolutely.**

Q. **How about the maxillary sinus?**

A. **This one, again, is sort of a cross between the previous two in terms of agreement. We have the same curve shape. We see a very rapid deposition phase. And we see a biphasic washout.**

Q. **So do you believe that this graphs shows deposition of Nasacort AQ in the maxillary sinuses for the 1996**

volunteers?

A. Yes. It's a lower percentage, of course, but there is definitely deposition there.

Q. Do you believe that it was retained for about an hour in those volunteers?

A. Yes. The curves are still decreasing after an hour. They are still level, no noise yet, or relatively little noise.

Q. And I guess the question of the day is, did you see it in the frontal sinus?

A. We have curves at the frontal sinus as well.

Q. So this is the three volunteers from 1996 study, deposition of the frontal sinus?

A. This is the actual data for the three volunteers from that study. We see very similar data for the maxillary sinuses. The uptake values are similar. Again, that rapid uptake. Again, a portion of it is washed out fairly rapidly, and another portion of it is washed out much more slowly. It's retained past an hour.

Q. Dr. Berridge, how do you know that this data past an hour is real data and not just an artifact?

A. Well, there is probably many things you can think of. But if you simply look at the curve, you see how the lines are relatively flat. When data has problems with it, you have noise in the data, and the data points bounce all over

the place generally. Sometimes toward the end of the activity, when the activity gets very low; the data corrections that are being done as part of the whole procedure, we didn't go into depth; cause the values to deviate wildly. This is staying very well behaved. The curve has the plastic-curved shape that you would expect. There is only one point that deviates away from the normal, which is really very good for PET data. And the decrease stays nice and well behaved. It has all the hallmarks of real PET data, just like every other region we had in the study.

Q. Okay. Let's talk about your second study now.

MS. BALDWIN: You can take that down, Eric?

BY MS. BALDWIN:

Q. When was the second PET study conducted?

A. 1998 is when I finished.

Q. And what was the purpose of your 1998 PET study of Nasacort AQ?

A. Well, it changed as we went along, actually. The actual purpose of the study was to look at a competitor's product because we had Nasacort AQ data and the competitor product was Flonase. It was chosen because of the marketing aspect basically, I think, but they wanted to know how it behaved relative to Flonase. So we started out to do a study of Flonase. We were asked to radiolabel the active

ingredient and do that formulation.
Q. And when did Nasacort AQ come into the study?
A. Very quickly, actually, because we started to see that the results that we were getting from the Flonase distribution in volunteers seemed to be different from that of what we had seen with the Nasacort AQ in the first study. And so it became of immediate interest to do a crossover study to try to get more data in those same volunteers of Nasacort AQ so that they could do it a direct comparison in a crossover design.
Q. Now, did you conduct that 1998 study in the same way you just described the 1996 study for us?
A. Yes, we did.
Q. So it was conducted with the same protocol they used in 1996?
A. Yes, it was the same protocol.
Q. Same PET scanner?
A. Same PET scanner, same institution, all the same personnel even.
Q. Same method of data analysis?
A. Well, we did change the data analysis. Most of the data analysis was the same, yes.
Q. Which part was the same?
A. All of the alignment. The initial treatment of the images was all the same. The only thing that was different

was the regions of interest.

Q. What regions of interest did you use in 1988?

A. We had some better computer power. We had a couple more years to write software. And since we were pioneering these studies, we were developing tools as we went along. And we wanted to get regions that would more exactly correspond to the anatomic regions for purposes of discussion.

Q. Could you show us what the regions of interest looked like in the 1998 study?

A. Yes. You almost have to see them, it's very difficult to describe. We have an image to show.

What you are seeing there, the translucent part is an MRI image in just low intensity of one of the volunteers in the study. Actually, I believe the volunteer is from the 2002 study. But it's a volunteer.

And then the regions are shown on that in different colors as we created them. They're three-dimensional images. They're three-dimensional regions. They're irregular in space because they conform with the outlines of the structures as those structures are identified on the MRI scan.

So you can see down here is what we call the mouth-throat region. It's the nontarget region.

Here is the frontal cavity. The nose is divided

into two regions, superior and inferior. We can see the turbinate regions behind there, at least some of them. We have the maxillary sinuses over there and the frontal sinus way up here by itself.

Q. You have never seen a nose in so much different ways, have you. Dr. Berridge, could you look at PTX-567 in your binder there?

A. Yes, ma'am.

Q. And what is that document?

A. That is tabular data from this study that we submitted to Aventis at the time.

Q. So that's the raw data that you get from the PET study?

A. Yes, it is. It's broken down actually into much smaller regions that were then grouped together into the regions that were recorded.

Q. And were the results of this 1998 study published?

A. Yes, they were. We published them in a paper that appeared in the Journal of Nuclear Medicine. I'm sorry. That was the first study. I misspoke. We published them in an abstract for this study that appeared, that went to the International Society For Aerosol Medicine.

Q. Is PTX-569 in your binder there, is that the abstract you are referring to?

A. That is indeed the exact display that we used for that

presentation.
Q. Were the results of the 1998 study consistent with those that you had seen in 1996?
A. Yes, they were consistent with 1996 results.
MS. BALDWIN: If we could pull up the graphs there? Thank you.
BY MS. BALDWIN:
Q. So these are the graphs of Nasacort distribution and kinetics from the 1998 study?
A. Yes, they are. We were trying to show pretty much all the data in the study in a limited space so it's rather busy, but that shows the average uptake at each time point as an average of volunteers in that study.
Q. Did this study show deposition of Nasacort AQ and retention for about an hour in the frontal cavity of the 1998 volunteers?
A. Yes. That is on the lower graph, those curves are there, and that shows clearly there is deposition.
Q. They show deposition and retention for about an hour in the turbinate regions for the 1998 volunteers?
A. Yes, they did. Definitely.
Q. How about the maxillary sinus?
A. Yes, that would be the upper panel. And we see uptake, we see deposition into the maxillary sinus, and we see retention past an hour.

Q. **How about the frontal sinus?**

A. **Yes, we do also see it in the frontal sinus.**

Q. **Did you see it in the frontal sinus for all the volunteers for 1998?**

A. **No. Actually, we did not. We saw it in three of the volunteers out of the five.**

Q. **Could you show us your graph of the volunteers from 1998?**

A. **We prepared a graph of that data. This shows the frontal sinus curve of each volunteer from that study separately.**

Q. **And how do you know that this is real data and not just an artifact?**

A. **Well, actually one of the nice features of this that helps us to decide that is that most of the ways that one could think of that could give you an artifact involve data spilling in from one of the other regions that have a lot of activity in it. A little spillover sometimes happen in PET. We were very careful, of course, in defining our regions in all of the studies to try to avoid that. Well, if that were to happen, you would see uptake in every volunteer because it would show you uptake even when there isn't any. You would not be able to measure the fact there is no uptake.**

But these two volunteers had no uptake. In these other volunteers, we see the nice curves shapes as we

did in the previous study. It's the exact same sort of data, behaves exactly the same way and, in my mind, it's perfectly trustworthy.

MS. BALDWIN: You can take that down, Eric.

BY MS. BALDWIN:

Q. Now, you conducted yet a third PET study of Nasacort AQ. Is that correct, Dr. Berridge?

A. We did indeed, yes.

Q. Was that PET study consistent with what we have seen for 1996 and 1998?

A. It was in the main consistent with all the conclusions we have made, yes.

Q. Did you see any differences in that study?

A. There was one difference with that study, really.

Q. And what was that?

A. That was the frontal sinus. In that study, we did not observe uptake into the frontal sinus in any of the volunteers.

Q. Did you observe any other differences in that study?

A. Well, the uptake patterns in general were pretty much the same but we had major problems with that study. We had very noisy data. We had inconsistent data. The data was erratic. It was a very problematic study for me.

Q. Dr. Berridge, as part of your work as an expert in this case, have you formed any opinions as to whether or not

Barr's ANDA product would behave in the same manner as we saw in your 1996 and 1998 PET studies on Nasacort AQ?

A. **Yes, I did form those opinions.**

Q. **And what was your opinion?**

A. **That the Barr product would behave the same as the Nasacort AQ does.**

Q. **What is the basis of that opinion?**

A. **Well, I reviewed all of the data that we had in all of these materials on the Barr product: the chemistry, manufacturing and controls information, the package insert information. And it's clear that all of the ingredients are the same, quantities are the same, the methods are the same. The instructions to the volunteers are the same, and the pump spray is the same. It has to behave the same.**

Q. **Dr. Berridge, if you could look at PTX-1 and PTX-3 in your binder in front of you.**

A. **Okay. I have that.**

Q. **Do you recognize those documents?**

A. **Yes, I recognize those.**

Q. **And what are they?**

A. **Well, number one is the patent that I was asked to look at, 5,976,573.**

Q. **And what was PTX-3?**

A. **And PTX-3 is the other of the two patents that I was asked to look at. This one is 6 -- my eyes are going**

funny -- 143,329.

Q. Dr. Berridge, were you asked to compare the claim limitation related to deposition and retention of the claimed formulation with Nasacort AQ?

A. Yes, I did.

Q. Did you compare those claim limitations related to deposition or retention with the results of your 1996 study?

A. Yes, I did with that, too.

Q. Were you also asked to compare those same claim limitations of the patents in suit with the Barr ANDA product?

A. Yes, I compared those with the Barr ANDA product as well.

THE COURT: Doctor, please keep your voice up.

THE WITNESS: Thank you.

THE COURT: Because people in the back of the courtroom need to hear you, too.

THE WITNESS: I'm sorry. I'm getting a little dry.

MS. BALDWIN: Dr. Berridge, there is a water right there.

THE WITNESS: I'll be okay.

BY MS. BALDWIN:

Q. Can we look at Claim 5 of the '573 patent.

And the phrase is: Deposit on the mucosal

surfaces of the nasal cavity. Was that one of the claim limitations that you have formed an opinion about, Dr. Berridge?

A. Yes, it was.

Q. Is it your understanding that pursuant to this Court's instruction that the term "nasal cavity" includes the anterior regions of the nose, the frontal cavity, turbinates which overlie the concha, maxillary sinuses and the frontal sinuses?

A. Yes, I was given that definition, and I used it.

Q. Did you form an opinion as to whether or not Nasacort AQ would meet this claim limitation?

A. Yes, I did.

Q. And what is that opinion?

A. That it does meet that claim limitation.

Q. And what is the basis of your opinion?

A. All of the data that we have just showed. That it does -- the data that I have from my own experiments show that it does deposit in each of those portions of the nasal cavity.

Q. Would Barr's ANDA product also deposit on the mucosal surfaces of the nasal cavity as defined by this Court?

A. I haven't been able to do the experiment, but I have to believe that it would because it's identical.

MS. BALDWIN: If we could look at Claim 25 of

the '329 patent.

BY MS. BALDWIN:

Q. **Here you see the claim limitations: Each of the mucosal surfaces of the anterior region of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conchas.**

Did you form an opinion as to whether Nasacort AQ meets that claim limitation, Dr. Berridge?

A. **Yes, I did.**

Q. **What was that opinion?**

A. **That it does meet that claim limitation.**

Q. **Did you also form an opinion as to whether Barr's ANDA product would also meet that limitation?**

A. **Yes, similar to what we just said. Because it's identical to Nasacort AQ, I have to believe that it will.**

Q. **Let's also look at another portion of Claim 5, and this wording is also found in Claim 25 of the '329 patent, so we can treat them together.**

And the limitation is resisting being cleared from the mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity.

Did you form an opinion as to whether or not Nasacort AQ would meet that claim limitation of Claim 5 of the '573 and Claim 25 of the '329 patent?

A. **Yes, I did form that opinion.**
Q. **And what is that opinion?**
A. **That it does meet that claim limitation.**
Q. **And what is the basis of that opinion?**
A. **Again, these are experiments that I performed myself. I was asked specifically by Rhone Poulenc Rorer essentially to evaluate this because what they wanted to know in the first place is whether their formulation resisted mucociliary clearance, whether it caused the drug to stay where the drug was sprayed as they put it to me. So that is what the study was designed to show us.**
Q. **How did the study show us that?**
A. **Because we knew going in that mucociliary clearance clears materials from the nose very rapidly and that it removes them from 10 to at the very most 30 minutes. So what we were looking for was a retention in the nose that was longer than that and would be longer than that probably from a clinical standpoint. So we weren't looking for small differences, we were looking for a large increase. So we were looking for increases for retention that might persist toward an hour, and we measured that. We saw that retention and, therefore, I have to conclude that that it does resist clearance by mucociliary action.**
Q. **Did you also form an opinion as to whether Barr's ANDA product would meet this limitation?**

A. **Yes, similar to my other opinions. That because it's identical to Nasacort AQ, it will behave the same way.**

MS. BALDWIN: Thank you, Dr. Berridge. I have no further questions.

THE COURT: You may cross-examine.

CROSS-EXAMINATION

BY MS. RURKA:

Q. **Good afternoon, Dr. Berridge.**

A. **Good afternoon, ma'am.**

Q. **How are you?**

A. **Quite well.**

Q. **So, Dr. Berridge, for the three studies in which you administered radiolabeled triamcinolone acetonide in the form of Nasacort AQ to 14 healthy subjects, how many of those -- eight of those subjects did not show uptake in the frontal sinus; correct?**

A. **That's a bad way to put it but, yes, that's correct.**

Q. **So Nasacort AQ does not always deposit in the frontal sinus?**

A. **It does not always deposit on the frontal sinus.**

Q. **Dr. Berridge, you are not an expert in nasal anatomy, are you?**

A. **I know something of it but, no, I don't call myself an expert.**

Q. **I guess you know something of it so let me ask you**

this. Is everyone's frontal sinus the same size?
A. I'm pretty sure there are significance variations in frontal sinuses, yes.
Q. And they're located in different areas from person to person in relation to the other nasal structures; right?
A. I could not tell you how much, no.
Q. But they are located in different areas, located in different areas in relation to the other nasal structures from person to person?
A. I'm not sufficiently expert to answer that.
Q. So you don't know?
A. No.
Q. Let's talk about the most recent study you conducted. That was the 2002 study. That was a randomized crossover study using Nasacort AQ and Flonase?
A. It was.
Q. That means that Flonase and Nasacort AQ were administered to the same six patients over a few days span?
A. Well, actually no. It was over more than just a few days span. It was administered to the same six patients, and it means that both were administered to each patient and that it was done in a random order.
Q. Okay. Let me ask you this: Was it done over a few days span? Was the study, the study from Nasacort AQ to Flonase, each subject done over a few days span?

A. **I believe it was in two weeks. I'm not sure exactly of the intervals.**

Q. **Actually, I've been saying patients. There were six subjects, healthy subjects. Correct?**

A. **They're actually normal volunteers. Patients is not quite the correct word to use.**

Q. **So I think you testified that you analyzed the data or maybe you didn't. You analyzed the data from the 2002 using the contoured regions of interests, not the cubes that you testified about, the 1996 study?**

A. **Correct.**

Q. **And then you assigned a region of interest to the frontal sinus using a region as well. I'm sorry. The region of interest you used to assign a frontal sinus was shaped like the patient or the subject's frontal sinus. Right?**

A. **It was shaped like the frontal sinus. It would have been somewhat larger than the frontal sinus because we were counting again for the that partial volume affect, a little bit of spillover that occurs in PET.**

MS. RURKA: Can you pull up Plaintiffs' Exhibit 5, please?

BY MS. RURKA:

Q. **And these are the results from your 2002 study. Is that correct?**

A. **This is the front page of the 2002 report, yes.**

MS. RURKA: I'm sorry. Did you get a copy of that? I apologize.

May I approach the witness?

THE COURT: You may.

(Documents passed forward.)

THE WITNESS: Thank you.

THE COURT: I think we have that, don't we?

MS. RURKA: You might have that.

THE COURT: I think we have that.

MS. RURKA: I'll save you the paper.

Pull up Page 12, please, Mr. Young.

BY MS. RURKA:

Q. **So, Dr. Berridge, you concluded that no uptake was observed in the frontal sinus on any of the six patients you studied in the 2002 study. Correct?**

A. **In the 2002 study, yes, that was my conclusion.**

Q. **I think you also discussed your 1998 study on direct examination. Right?**

A. **I did.**

MS. RURKA: May I use the Elmo?

BY MS. RURKA:

Q. **Okay. Ms. Baldwin put up Plaintiff's Demonstrative Exhibit 181 for you to analyze the data from the 1998 study with respect to frontal sinus. Do you recognize this?**

A. **I recognize that, yes.**
Q. **Okay. And that shows that two subjects in the 1998 study did not have frontal sinus uptake. Right?**
A. **That is my interpretation, yes.**
Q. **Okay. And of the three subjects that you observed as having frontal sinus uptake, the highest you got was .5 percent of the administered dose. Is that right?**
A. **That is correct.**
Q. **And the other two were under .2 percent. Right?**
A. **Also correct.**
Q. **And do you have any evidence that the less than .5 percent that was shown in any of these three subjects had any sort of therapeutic effect for those subjects?**
A. **My studies were not designed to look at therapeutic effect in any way. I have no opinions on therapeutic effect.**
Q. **So you don't know whether or not the .5 that was shown in the one patient had any therapeutic effect on the other?**
A. **No.**
THE COURT: He said he doesn't have an opinion. Counsel, we can move on to the next question.
MS. RURKA: Can we go to the 1996 study?
BY MS. RURKA:
Q. **You tested three subjects of Nasacort AQ in the 1996 study. Right?**

A. **That's correct.**
Q. **And that was a pilot study? That was the first study you did?**
A. **That was the first study, yes.**
Q. **And that study was designed to determine the distribution and extent of drug in the regions of interest. Right?**
A. **Almost. It was designed to determine the regional deposition and kinetics of the drug.**
Q. **You reported that in the 1996 study, 2.97 percent to about 3.5 percent deposition of the frontal sinus for the three subjects. Right?**
A. **I can't verify those numbers siting right here but it sounds pretty close, yes.**
Q. **Would you like me to help you? Would you like to see the study?**
A. **Okay.**
Q. **It might be in your binder?**
A. **Probably yes.**
MS. RURKA: And yours, too, Your Honor.
So could you pull up the exhibit, Mr. Young? Thank you.
And Page 9, Defendants' 6.
MS. BALDWIN: PTX-529, if you can't find it.
MS. RURKA: Yes, that would be PTX-529 in your

binder.

THE WITNESS: Okay. Good.

BY MS. RURKA:

Q. And that table shows for each of the volunteers are on the left side. Right? And the frontal sinus region shows percent uptake in the frontal sinus. PDmax would be the percentage uptake in the frontal sinus that you observed, the maximum?

A. Yes, that stands for percent maximum.

Q. So you have 3.5, 3.5 and 2.97. Right?

A. That's correct.

Q. And I believe you said in the 1998 study, the highest you showed was .5 percent. Right?

A. That is what we saw, yes.

Q. You published the results of the 1996 study. Right?

A. We did.

Q. In the Journal of Nuclear Medicine?

A. That's correct.

Q. That is a well regarded journal in the field of positron emission tomography?

A. It's probably the most respected in this sort of work, yes.

Q. So when you published results in the Journal of Nuclear Medicine, it's important that you published accurate results. Correct?

A. **I believe so, yes.**
Q. **I think you testified that you used 1.8 centimeter cubic regions of interest in the 1996 study to assign the radioactivity to the nasal anatomy. Correct?**
A. **We did.**
Q. **And no cubes in the assignment that showed radioactivity were left unassigned. Right? To a particular nasal region.**
A. **No, nothing was left unassigned. And we accounted for all of the deposited dose.**
Q. **And you also testified I believe that some of those cubes could overlap from one anatomical region to another. Right?**
A. **Yes, that's true.**
Q. **And if you had such an overlap, you could conceivably attribute radioactivity to a region in the nasal anatomy in which there actually was no radioactivity. Correct?**
A. **That is a difficult one to say yes or no.**
Q. **Okay. Well, Dr. Berridge, when you had an overlap, I think you testified earlier that when you had an overlap between the frontal sinus and an adjacent region, for example, the frontal cavity or the turbinate, that if there was an overlap, that you would assign that to a turbinate region or the adjacent region rather than the frontal sinus region. Correct?**

A. That's right. That's what makes it difficult. It depends on what regions we're specifically talking about.

Q. Okay. So in that situation, if the deposit was in fact in the frontal sinus, you would have assigned it to the wrong region. You would have assigned it to a region where the radioactivity was not in effect?

A. No, you see, because what you do in that situation is that one region -- say that it overlapped with the frontal sinus and with the upper part of the frontal cavity. You would assign that cube to the frontal cavity and, therefore, you take the risk of assigning frontal sinus data to the frontal cavity region that already had much more but you would avoid the risk of assigning frontal cavity data to the frontal sinus and making it look as if material was there when it was not.

Q. I'm sorry. Dr. Berridge, maybe you misunderstood. That is exactly what I was saying. You said that you had, any overlap with the frontal sinus and an adjacent region like the frontal cavity, you would assign whatever activity was in that cube to the frontal cavity even if it was in the frontal sinus; right?

A. If there were dual regions in that case, yes, we would do that.

Q. Okay. So your results, your frontal sinus results would not be accurate. They would be understated. Right?

A. **Actually, it would be possible, yes.**
Q. **And your frontal cavity results would be overstated. Right?**
A. **Well, that's probably not true, no, because the frontal cavity results, the number in the frontal cavity is sufficiently large to spill over from the frontal sinus into it and would be insignificant.**
Q. **It still would be overstated. Right?**
A. **No, it's not right.**
Q. **The percentage would not be overstated?**
A. **No. The amount that would be added to the frontal cavity is so small that it doesn't significantly change that number. That number hasn't changed, really, at all. When you do the analysis, you have a certain amount of variability, and you have not changed your final number. It would not be overstated.**
Q. **So your testimony is it would never be overstated?**
A. **In the example we are talking about right now, no, it would not.**
Q. **Are you saying that you never overstated the assignments in an adjacent region of the frontal sinus in the 1996 results?**
A. **I am sorry, can you repeat that.**
Q. **I am sorry. That was a very badly phrased question.**
So your testimony -- do you have any of the data

from the 1996 study showing how you assign these cubic regions of interest?

A. **We don't have the -- the assignments, no, did not survive to today.**

Q. **What we have is your testimony that you assigned these regions carefully to make sure that you weren't reporting results in the frontal sinus that weren't, of course, in the frontal sinus. Right?**

A. **We do have that testimony, yes.**

Q. **And that's the only thing we have. Right?**

A. **Well, no, it's not the only thing we have.**

Q. **It's not reported in your 1997 journal article, is it?**

A. **Well, to come to that conclusion we also have the data that we just showed. If that were a systematic problem, if that assignment were happening, then you would always see uptake in the frontal sinus.**

Q. **That is if you had assigned the cubic regions the way you said you assigned the cubic regions. Right?**

A. **Well, of course.**

Q. **What I am talking about is how you assigned the cubic regions, we don't have any report of how you assigned those regions other than your testimony?**

A. **No, we don't.**

Q. **And you didn't put it in your 1997, or the Journal of Nuclear Medicine paper, did you?**

A. **We did describe the regions and how they were done, yes.**

Q. **You didn't describe how you assigned anything that was overlapping from one region to another to the adjacent region that had higher activity, did you?**

A. **Actually, without reading the paper, I couldn't tell you for sure. But I don't believe we did, no.**

Q. **And you didn't report it in your 1996 final study report, either?**

A. **No, we really didn't go into all of the logic about the assignment of each region.**

Q. **Okay. So you could have understated the frontal sinus deposition in the 1997 Journal of Nuclear Medicine paper, I think it was the 1998 Journal of Nuclear Medicine paper, but no one would know that because it was not recorded how you assigned the regions of interest in the 1996 study. Right?**

A. **That's an interesting situation. Okay, I will say right.**

Q. **And in the 1998 study, when you got those results, you got two out of the five subjects with, according to your testimony, no frontal sinus uptake. Right?**

A. **Yes, that's correct.**

Q. **When you got those results, you didn't go back and reanalyze the 1996 study results to see if there was some sort of factor contributing to the difference between the**

two studies. Right?
A. Actually, we did think about it, and we didn't see anything that we thought needed to be altered.
Q. So you didn't think reporting results of three to four percent in a Journal of Nuclear Medicine paper, uptake in the frontal sinus -- I think you testified that you found those results surprising. Right? Or unexpected?
THE COURT: Counsel, ask one question. Okay?
MS. RURKA: Sorry.
BY MS. RURKA:
Q. Okay. You found the results in the 1996 study unexpected. Right?
A. We were initially surprised to see deposition in the frontal sinus, if that's what you mean.
Q. Right. And you reported results of three to four percent in the Journal of Nuclear Medicine paper in the 1996 study?
A. Yes. We report what we find.
Q. And you found zero percent in two of the subjects in the 1998 study?
A. That's correct, too.
Q. And that didn't cause you to question whether the results of one of those two studies might be out of whack?
A. Well, no, it didn't. It more caused me to wonder where the sources of the variability are.

Q. **Did you report the zero finding in the two subjects in the 1998 study anywhere?**

A. **I am sorry. The zero uptake in the 1998?**

Q. **Yes. I am sorry. The zero uptake in the frontal sinus?**

A. **That was included in the data on the poster.**

Q. **Was it included that you found two of the five subjects showed no frontal sinus uptake?**

A. **Probably not. The frontal sinus was almost an afterthought at that stage in the game. We were not really concerned with it.**

Q. **Okay. I am sorry. You found it unexpected in the 1996 study. By the 1998 study you weren't concerned about the frontal sinus data anymore?**

A. **No. We were reporting the uptake in it. But we were not concentrating on it. The regions that were of most interest were the frontal cavity and the turbinates. So we reported the data, but we didn't go into great detail about the frontal sinus data in those reports.**

Q. **You didn't report anything on the 2002 study, which showed no uptake in the frontal sinus in any of the six subjects?**

A. **No. That work was unpublishable.**

Q. **Why was it unpublishable?**

A. **The data was just bad.**

Q. **Okay. You didn't say anything about the bad data in the 2002 study report, did you?**

A. **Well, the 2002 study report back to Aventis, which was the sponsor, was a report that I needed to present back to them to fulfill the contract, to report on all the work that was done. And I reported the bad data to them, yes.**

Q. **I am sorry. You reported that the data was bad for Aventis. Is that what you are saying?**

A. **I reported in that final report, which you just mentioned, yes, I reported all of that data back to them. But we were unable to draw conclusions from that data.**

Q. **And you were unable to draw conclusions from that data because of, you think it was bad data?**

A. **It was highly variable data. It had some very interesting patterns in it that just didn't really make sense. It was impossible for me to analyze properly.**

Q. **But none of that is in your 2002 final study report, is it?**

A. **I gave that report back to Aventis. I did the best job I could of presenting them the data and showing them what happened. It's in there. You do a study for someone and you report the results to them. You don't really want to come down on it too hard. But you report the results as they were. And they are in there.**

Q. **But you didn't publish anything on your findings on**

the frontal sinus data in the 2002 study in view of the fact that you reported three to four percent in the 1996 study. Right?

A. **Well, again, I was not focused on the frontal sinus. I did report the data, yes.**

Q. **So your 1996 study showed seriously different data than the 1998 study and 2002 study when it came to frontal sinus uptake. Right?**

A. **When it comes to the frontal sinus alone, there are differences between all of the three studies, yes, that's true.**

Q. **And you did nothing to bring this issue to the attention of the scientific community and submit perhaps another article in the Journal of Nuclear Medicine to explain the differences between the three studies?**

A. **No, I did not. The uptake in the frontal sinus of an anti-inflammatory steroid among three PET studies is not an issue of such burning importance that I would think that that paper would get accepted at any journal.**

Q. **Dr. Berridge, did you say anywhere in your 2002 final study report that the data cannot be trusted?**

A. **I said I couldn't analyze that data and come up with conclusions. There were problems with the data. And I did put that down, yes.**

Q. **I think you said that -- you did come up with a**

conclusion about frontal sinus data. Right?

A. **I reported there was zero uptake.**

Q. **So you did have some conclusions about the data in the 2002 study?**

A. **Well, yes, it wasn't totally worthless, no.**

Q. **Dr. Berridge, you did no studies on Barr's ANDA product. Right?**

A. **No. I have never had a sample of that product.**

Q. **Can we put up -- you reviewed Dr. Lockhead's viscosity testing results in reaching your conclusions about infringement for Barr's ANDA product. Right?**

A. **Yes, I saw viscosity results.**

Q. **Defendant's Exhibit 25. I just pulled up some of his data and put it in a usable format.**

Does this look like the viscosity results that Dr. Lockhead acquired for some of Barr's ANDA product that you reviewed in reaching your infringement opinion?

MS. BALDWIN: Objection, Your Honor. He doesn't have Dr. Lockhead's data memorized, nor is he an expert in viscosity or rheology.

THE COURT: Counsel, your reaction?

MS. RURKA: I have the actual reports here from Dr. Lockhead.

THE COURT: Has he been asked to analyze this information heretofore?

MS. RURKA: Yes. It was in his opening expert report.

MS. BALDWIN: Objection, Your Honor. All he said is he relied upon the opinions of Dr. Lockhead. He did not analyze this data. That was beyond the scope of his expertise.

MS. RURKA: Actually, Dr. Berridge reached the conclusion looking at Dr. Lockhead's data that it had the same thixotropic profile and the same viscosity profile. These two properties had the same thixotropic profile and the same viscosity profile based on the data he looked at from Dr. Lockhead. Dr. Lockhead did not express that opinion. So Dr. Berridge did analyze these data.

THE COURT: We will see what Dr. Berridge has to say.

MS. BALDWIN: Your Honor, we want to object to the exhibit because it inaccurately reflects the actual shear viscosity for the Barr ANDA product.

THE COURT: You object to the demonstrative?

MS. BALDWIN: Yes.

MS. RURKA: We can just use Dr. Lockhead's report.

THE COURT: You can take that down.

MS. RURKA: If you can pull up Defendant's Exhibit 362. If you can pull up Page 9 and 10 as well.

BY MS. RURKA:

Q. **Dr. Berridge, are these the data you reviewed in reaching your infringement opinion, the viscosity testing of Barr's product?**

A. **Yes. This is his report. I relied mainly on his conclusions, I must say.**

Q. **Okay. Well, I think, actually, it probably would help if you pulled up Defendant's Exhibit 314, which is Dr. Berridge's opening -- no, I am sorry, 313, which is his opening expert report?**

MS. BALDWIN: Can I have a copy?

MS. RURKA: Yes.

BY MS. RURKA:

Q. **Actually, Dr. Berridge, I believe you testified on direct that you thought Barr's ANDA product was identical to Nasacort AQ. Is that right?**

A. **Yes, I believe that.**

Q. **Why don't you go back to 362 at 9 and 10.**

A. **Okay, I see that.**

Q. **The data in the left-hand column are the viscosities of Barr's ANDA product. The first three -- six products are Barr's ANDA products, different batches of Barr's ANDA products. Right?**

A. **Yes, that appears to be correct.**

Q. **Then the last two are Nasacort AQ, setting and shear**

viscosity values?

A. Yes, they are.

Q. So Agis industry Point No. 002 shows apparent viscosity, setting viscosity at the top of 455 through 404. Right? Centipoise?

A. I am sorry. I was looking at the torque. Okay. Let me see. Now that I am there, can you say that again.

Q. The top right, the right column at the top, that's Agis Industry, which is Barr labs ANDA product, setting viscosity is from 404 to 455 centipoise. Right? It's right up on the screen, too?

A. All right. But I am looking on the paper and I am seeing a fairly wide range of numbers in that column.

Q. Okay. Why don't we pull up -- we will do it this way: We will pull up the setting viscosity for No. 002, that's Batch No. 002, Batch No. 003, and Batch No. 004.

A. Yes.

Q. If you look at all three of them. So you have setting viscosities of -- just the settings, please.

A. Okay, those are shears.

Q. So the setting viscosity for Barr's product ranges anywhere from 404 to 606 centipoise. Right?

A. Okay. Yes, it does. I apologize, I was just getting used to this table, again, because I said I relied on his conclusions, not on his data.

Q. There is a lot of numbers in here. The Nasacort setting is between 405 to 437. Right?
A. It does appear to be, yes.
Q. Are these numbers identical?
A. They very well could be. I don't know.
Q. Why don't we pull up the shear -- so it's your opinion that 404 to 606 is identical to 405 to 437?
A. It depends on the sort of normal variability that you get when you do this sort of measurement and what sort of overall range you get among a lot of products. It could be that there is no significant difference whatsoever between these numbers. I really -- I think you probably should address this question to him, not to me.
Q. Well, let's just circle, to circle the square --
THE COURT: Let me see counsel at sidebar, please.
(The following took place at sidebar.)
THE COURT: You are spending a lot of time in an area where he says that he didn't examine the data. He said he relied on the conclusions. Can you tell me why you persist in examining this witness in this regard?
MS. RURKA: I am sorry. I should have brought this to your attention. This is Dr. Berridge's report. He says he had reviewed the analysis conducted by Dr. Lockhead, that they exhibit the same viscosity profile and have the

same thixotropic property. Dr. Lockhead does not express an opinion that they have the same viscosity profile or exhibit the same --

THE COURT: I think you can get to that point a lot quicker than you are doing. We have only a limited number of days here.

MS. RURKA: I apologize, Your Honor.

THE COURT: The other thing. Counsel should keep in mind that this is a lay court, and while you may be steeped in the technology, I am to an extent, but to the extent that you have educated me. It is not my background. I don't know if you are a chemist or if you are. But you might want to keep that in mind. You have been living this. I have been living a lot of other cases.

(End of sidebar conference.)

BY MS. RURKA:

Q. Please pull up Defendant's Exhibit 358 at Page 27.

Why don't you pull up the first page. This is your opening expert report, Dr. Berridge?

A. Okay. Yes, thank you.

Q. On Page 27, you state that, under B, that you have reviewed the analysis conducted by Dr. Lockhead, that the accused Barr product exhibits the same thixotropic property as Nasacort AQ. Right?

A. Yes, I do say that.

Q. **You also say you reviewed the analysis conducted by Dr. Lockhead that the accused Barr Laboratories product exhibits the same viscosity profile?**

A. **Yes.**

Q. **Did Dr. Lockhead actually say that Barr Laboratories' product has the same thixotropic properties as Nasacort AQ in his expert report?**

A. **One thing I was looking at was No. 15 in his report, which indicated that his viscosity results confirmed his own -- Barr's reports of viscosity results confirmed his own testing and indicate that Barr's proposed ANDA product has viscosities that are within the specific setting of viscosity and shear viscosity ranges set forth in the patents.**

That, to me, indicates both, that is, when you put the two together, as far as I understand it -- and I readily admit not to being an expert in this area -- that that produces, that comes to the conclusion that the thixotropic properties are also the same. Plus the fact that I reviewed myself all of the ingredient information, and that the ingredients are identical. If the ingredients are identical and the testing results are different, then you have to wonder about variability in manufacturing. Not on differences in the formulation.

Q. **You didn't review the manufacturing process for both**

of these products, did you?
A. I saw the CMC information and I saw the package insert information, that the compositions are identical.
Q. You didn't see any manufacturing data or information on the size of the product, did you?
A. I believe that the CMC information is manufacturing data, yes.
Q. It is data on the manufacture of the Barr product?
A. Yes.
Q. You reviewed that?
A. I saw a CMC section at some point, yes.
Q. You don't know whether or not Barr's ANDA product is manufactured in the same way as Nasacort AQ, do you?
A. Techniques of manufacture and types of machines and that sort of thing, no. But the composition is the same.
Q. So Dr. Lockhead never said anywhere in his expert report that they have the same thixotropic properties. Right?
A. I believe what he has said here is tantamount to the same thing, yes.
Q. He never said same thixotropic property?
THE COURT: He didn't use those words, counsel. But this is the witness' answer.
BY MS. RURKA:
Q. He never said anything about the same viscosity

profile, either, did he?
A. My understanding is that, after I read his report, my understanding was that it has the same thixotropic properties and the same viscosities, which is not surprising if it has the same composition. And that was what I based my opinion on.
Q. But you don't know whether any of the differences in the viscosity profiles that we were looking at earlier might cause a difference in frontal sinus deposition, do you?
A. I think I would not expect them to cause any difference in frontal sinus deposition.
Q. You don't have any experience in formulating thixotropic suspensions, do you?
A. Well, no. But I have observed Flonase deposition.
Q. What did Flonase deposition show?
A. There was less Flonase deposition in the frontal sinus, but there was some.
Q. So Flonase did deposit in the frontal sinus?
A. A little bit, in fewer be patients, in fewer subjects.
Q. In two subjects. Right?
A. Not as successfully, but it did get there.
Q. It is your opinion that it got there in two subjects. Right?
A. I believe that's what the data was, yes.
Q. Out of the, I think, 12 that were studied?

A. **Well, I discount the data from 2002, with because I don't put that in the same -- I don't believe that is really comparable data, but, yes.**

MS. RURKA: I have no further questions.

THE COURT: Redirect.

REDIRECT EXAMINATION

BY MS. BALDWIN:

Q. **Dr. Berridge, Ms. Rurka spent a lot of time talking about your 2002 study. Let's talk about that a little bit. First of all, you mentioned that you did tell RPR that you had issues with the data from the 2002 study. That's what you said. Correct?**

A. **Yeah. I can't recall the specific language. But, yes.**

Q. **Well, I will help you out, just assist you. In PTX-351, it's Berridge 16.**

A. **That's the final report from that study.**

Q. **Final report from your 2002 study. If you look at the -- look at that first sentence under Results Summary. What does that sentence say, Dr. Berridge?**

A. **The study showed several trends in the data, but due to unusual variations between observations from the individual subjects, the observed differences did not reach statistical significance.**

I am speculating it could be combined with the

previous data. I was trying to put a happy face on it.
Q. So you didn't bury your concern about the data somewhere in the report, you put it right up there in the very first sentence of the Results Summary, didn't you?
A. Well, yes.
Q. What did you mean by the variability? First of all, what was the purpose of this 2002 study?
A. Well, you know, I wondered that. But it was essentially a duplication of the 1998 study. I was never really told. In fact, when I was approached and asked to do this study, I responded that we have already done this study. Are you sure you really want to go ahead and do it? And they said, yes, absolutely, this is what we want to do.
My belief is that they wanted to gather more subjects, get more data, try to show more strongly the differences between Nasacort AQ and Flonase. And that, perhaps thinking that we have more experience now, we will get a better study, we may be more controlled, have better-behaved data, more tightly clustered data, and come up with something that's more striking in terms of measuring the difference between those two products.
Q. So did you conduct this study in the exact same way that you conducted the 1998 study?
A. All our methods really were the same as much as we could make them, yes.

Q. **So you used the same protocol as you used in 1998 and 1996. Correct?**

A. **Same protocol all the way through, yes.**

Q. **Same alignment procedures used as in your previous two studies?**

A. **Correct.**

Q. **Same people conducted the study?**

A. **Yes.**

Q. **Did you see the same results?**

A. **No.**

Q. **So when you talk about variability in the data, could you please explain to us what you mean by that? Do you have an example you could show us?**

A. **You have to see the data to understand that. Variability is a term that people instinctively understand but perhaps in this case -- can we show some of the curves?**

Q. **Okay. So this is what we expected to see. Correct? We talked about this earlier. This is what you would expect to see from the data. Correct?**

A. **That is the stylized ideal curve, yes.**

Q. **Okay. And when we talked earlier, is that what you saw in 1998 for, say, the lower frontal cavity?**

A. **We saw that same general shape in '98 for most of our regions, most of our volunteers, yes.**

Q. **So this was your data of all the volunteers in 1998.**

Correct?

A. **That is each volunteer, yes, from the 1998 study plotted individually. There is some nice clustering agreement among the Nasacort AQ data as far as PET standards go at least. The Flonase is perhaps a little more spread out than I would like but it always has been throughout all these studies, but it shows the same general curve shape. We have two clusters. It's analyzable data.**

Q. **So what did you say in 2002?**

A. **We'd have to look at it.**

Q. **Wow! That doesn't look quite the same.**

A. **There is a strange jumping around of data points that we have not seen in prior studies which I, to this date, don't understand. The main problem in trying to analyze this data, though, is that each of the two drugs broke up into two different groups. If you look at that, you see the upper group there and a lower group. You have Flonase's cluster here. You have a gap. You have more Flonase coming in down here. You have two groups of subjects with the same drug that are behaving differently with no reason that we know of behind it. And then the same thing happened with the Nasacort AQ. Plus all of this random motion around that we had not seen previously.**

Q. **Now, is this the only region that you saw this sort of variability?**

A. **We saw it throughout the study.**

Q. **Could you show us an example? We took the lower. Just pick something higher.**

A. **Yes. In order to try to get two representative regions and not waste a lot of time, we pick the lower and upper of the ones that make a difference to us. So this would be the superior turbinates.**

Q. **So this is 1999 data for the superior turbinate region?**

A. **This is the 1998 data. This is part of the motivation why we might want to do it again in 2002. This is not ideal either. However, we still have a bit of a group. We're breaking up even a little bit with the Nasacort AQ. I was not terribly happy with that, but it got worse in 2002.**

Q. **And what did the 2002 look like?**

A. **It looks like noise. There is the same general curve shaped buried under there, but I have a real hard time trying to come to conclusions with that. And in Flonase's case, we have several subjects that are way down in the third, even in the superior turbinates, not to mention something like the frontal sinus. It was just a very difficult data set.**

Q. **So if you used all the same procedures and the same people conducted in 2002, what was different about this study than your previous ones?**

A. **Well, there was really only the one difference which caused perhaps several smaller differences. In this study, we performed the scans offsite. Previously, when we have done scans, we had a laboratory institution. We had a PET scanner essentially next-door in the same institution. And we did the study there. The volunteers were indoors.**

In this study, for reasons that probably don't bear going into, the scans were done on mobile PET units: a regular semitrailer with a PET camera mounted on it. And this is being done clinically routinely across the country these days. These scanners were coming in and being used in several hospitals in the area. And we just got a much better arrangement for scheduling as well as financially with people that had these scanners. That's why we choose to do them on these units. So we were shipping the drug offsite from where it was being manufactured, driving it to the site of the truck and then doing the scan on the mobile scanner inside the truck.

Q. **So when you are talking about shipping the drug, are you talking about the radiolabeled drug?**

A. **The radiolabeled material. Prepared in the canister. The formulated Nasacort canisters and Flonase canisters.**

Q. **So you prepare it in the lab and then you would ship it to this mobile PET scanner unit?**

A. **I put it in my trunk and drove.**

Q. **And drove down the block?**

A. **It was -- well, one site, it was a 20 to 40 minute drive across town.**

Q. **And why would that matter?**

A. **Well, really, at the time we didn't think it would matter at all. And that's why we designed the study that way.**

And even after this data came out, I still didn't see anything in that that explained it. It's really only been this year, it's really only been after receiving Professor Siegel's report and having to think about some of those issues, go back and revisit and try to come up with explanations, it was the end of a long line of reasoning. But I think that was it: It was cold. It was the dead of winter in Cleveland. And the drug got chilled while we were driving there.

There is also the fact that the truck was a little different. The scanner was a different scanner. The device that we were able to use to hold the volunteer was a little different. It wasn't that rigid thing we saw in the picture earlier. It was a more spidery contraption of plastic that we put inside the bore of the camera because we were constrained by space on the truck.

The volunteers were more constrained because the beds do not move back any farther. I don't think, I didn't

think we had motion artifacts, but that is perhaps a reason. I don't really believe that.

Also, it was cold. The volunteers came in cold. And in hindsight, perhaps that has an effect on what goes on up in the nasal anatomy.

Q. Do you remember the patients' reactions to the colder radiolabeled drug?

A. Yes, they noticed it. Most of the time, we didn't get any feedback from volunteers when they took the drug. The only thing was that reaction that they've just had a bouquet of roses shoved up their nose when they got the Flonase. That was the only negative comments we got from them generally. But in this case, they were responding that it was cold. At least in several cases, they felt that cold go in. Because of the short half-life of the material, we were more focused on getting the material in and getting the experiment started before the material decayed. Carbon 11 has a 20 minute half-life. You have to move quickly. So we didn't think about the fact that maybe we should stop and warm it up first.

I'm not really sure of the causes. All I really know for sure is that these things were different. What effect they have, I don't know, but I know I have data that I could not publish.

Q. Just one last question for you, Dr. Berridge. By your

1996 study, now, counsel referred to that as a pilot study. What was the purpose of that 1996 study?

A. Well, RPR came to us and said that they had this formulation and it was meant to cause the drug to stay on the nose longer than mucociliary clearance, and they wanted to know if that would happen.

The funding was limited. We could only do four subjects. We enrolled four. One didn't complete, so we have three subjects worth of data. That usually makes it a pilot study. When you go to publish it, that is a good thing to put in there to explain why you don't have so many subjects and don't get your paper rejected.

Part of the reason why it was limited like that is that the management at RPR had not completely become convinced that PET scanning was going to be a valuable thing to do, and they didn't want to commit to a larger more time consuming, more expensive study. So that is how we did that.

Q. If you hadn't been limited in volunteers, would you have done anything different in the 1996 study, would you have done it differently if it hadn't been a pilot study limited by volunteers?

A. I might have enrolled more volunteers. After we saw the data from the first few, though, we were pretty happy with what we were seeing. We didn't feel we needed any

more. We could not possibly have done anything different from the point of view of our techniques, our procedures.

Q. In fact, those same techniques are what you used in the 1998 and 2002 studies as well. Correct?

A. All except for how we did the regions, yes.

MS. BALDWIN: No further questions.

THE COURT: Thank you.

Thank you, Dr. Berridge. You are excused.

MS. RURKA: Your Honor.

THE COURT: Counsel, that's it for the day. We'll resume at 9:00 o'clock tomorrow.

I want to offer counsel a bit of advice. In terms of the actual presentation of your expert witnesses who are I'm sure all learned and expert in their fields of endeavor, that it is helpful if you keep in mind how you might present this sometimes technical information -- not so much the last witness. But just when using terms of art and terms that are not necessarily familiar with someone who has not studied. For instance, I'm not a medical doctor. When I interrupted Dr. Kaliner, I believe it was -- I forget the term, but it meant smooth. When you are preparing your witnesses, I don't blame the experts, I blame the lawyers for not properly preparing the witnesses to testify to a lay court; okay? Keep that in mind.

All right. We'll see you at 9:00.

(Proceedings adjourn at 5:00 p.m.)